

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041157 A2

(51) International Patent Classification⁷: **A61K**
(21) International Application Number:
PCT/US2003/029167

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(22) International Filing Date:
15 September 2003 (15.09.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/410,839 13 September 2002 (13.09.2002) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/410,839 (CIP)
Filed on 13 September 2002 (13.09.2002)

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Published:
— *without international search report and to be republished
upon receipt of that report*

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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: GROUP B STREPTOCOCCUS VACCINE

(57) Abstract: This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.



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GROUP B STREPTOCOCCUS VACCINE

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This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/410,839, filed September 13, 2002, which application is incorporated herein by reference in its entirety.

TECHNICAL FIELD

10 This invention relates to polysaccharides from the bacteria *Streptococcus agalactiae* (GBS) and to their use in immunisation.

BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or “group B streptococcus”, abbreviated to “GBS” (Ref. 1) is now known to cause serious disease, bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated.

The “B” in “GBS” refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into at least 9 serotypes (Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII) based on the structure of their polysaccharide capsule. In the past, serotypes Ia, Ib, II, and III were equally prevalent in normal vaginal carriage and early onset sepsis in newborns. Type V GBS has emerged as an important cause of GBS infection in the USA, however, and strains of types VI and VIII have become prevalent among Japanese women.

The genome sequence of a serotype V strain 2603 V/R has been published (Ref. 2) and various polypeptides for use as vaccine antigens have been identified (Ref. 3). The vaccines currently in clinical trials, however, are based on polysaccharide antigens. These suffer from serotype-specificity and poor immunogenicity, and so there is a need for effective vaccines against *S. agalactiae* infection.

It is an object of the invention to provide further and improved GBS vaccines.

DISCLOSURE OF THE INVENTION

The inventors have realised that saccharide-based vaccines can be improved by using them in combination with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS polypeptide antigens and (ii) one or more GBS saccharide antigens. The polypeptide and the polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover two or more GBS serotypes (*e.g.* 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and saccharide antigens may or may not overlap. For example, the polypeptide might protect against serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred combinations protect against the following groups of serotypes: (1) serotypes Ia and Ib, (2) serotypes Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and VII, (15) serotypes Ib and VIII, (16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VIII, (22) serotypes III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VII, (26) serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII, (30) serotypes IV and VIII, (31) serotypes V and VI, (32) serotypes V and VII, (33) serotypes V and VIII, (34) serotypes VI and VII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

Still more preferably, the combinations protect against the following groups of serotypes: (1) serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5) serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens. Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens.

Preferably, the immunogenic composition comprises one or more serogroup V antigens or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358,

GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the composition comprises a composition of at least two of these GBS antigens or a fragment thereof.

In one embodiment, the immunogenic composition comprises a GBS saccharide antigen and at least two GBS polypeptide antigens or fragments thereof, wherein said GBS saccharide antigen
5 comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or a fragment thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

10 Preferably, the combination comprises GBS 80 or a fragment thereof. In one embodiment, the GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the antigen group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80
15 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

Still more preferably, the combination is selected from the antigen group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS
20 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147. Even more preferably, the combination comprises GBS 80 and GBS 691.

In one embodiment, the composition comprises a combination at least three GBS polypeptide antigens. Preferably, this combination comprises GBS 80 and GBS 691.

Preferably, the immunogenic composition further comprises a GBS polypeptide or a
25 fragment thereof of serogroup II.

The polypeptide antigen

The polypeptide is preferably: (a) a polypeptide comprising an amino acid sequence selected from the group consisting of the even-numbered SEQ IDs 2-10966 from Ref. 3; (b) a polypeptide comprising an amino acid sequence having sequence identity to an amino acid sequence from in (a);
30 or (c) a polypeptide comprising a fragment of an amino acid sequence from (a).

Within (a), preferred SEQ IDs are those which encode GBS1 to GBS689 (see Table IV of reference 3).

Within (b), the degree of sequence identity may vary depending on the amino acid sequence (a) in question, but is preferably greater than 50% (e.g. 60%, 70%, 80%, 90%, 95%, 99% or more).

35 Polypeptides within (b) include homologs, orthologs, allelic variants and functional mutants of (a). Typically, 50% identity or more between two proteins is considered to be an indication of functional

equivalence. Identity between proteins is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1.

Within (c), the length of the fragment may vary depending on the amino acid sequence (a) in question, but the fragment is preferably at least 7 consecutive amino acids from the sequences of (a) *e.g.* 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more. Preferably the fragment comprises one or more epitopes from the sequence. Other preferred fragments are the N-terminal signal peptides of SEQ IDs 1-10966 from Ref. 3, SEQ IDs 1-10966 from Ref. 3 without their N-terminal signal peptides, and SEQ IDs 1-10966 from Ref. 3 wherein up to 10 amino acid residues (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues) are deleted from the N-terminus and/or the C-terminus *e.g.* the N-terminal amino acid residue may be deleted.

The polypeptides can, of course, be prepared by various means (*e.g.* recombinant expression, purification from GBS, chemical synthesis *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal or host cell proteins) or substantially isolated form.

Preferred polypeptide antigens are: GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691, including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The nucleotide and amino acid sequences of GBS80 in Ref. 3 are SEQ ID 8779 and SEQ ID 8780. These sequences are set forth below as SEQ ID NOS 1 and 2:

SEQ ID NO. 1

ATGAAATTATCGAAGAAGTTATTGTTTTTCGGCTGCTGTTTTTAACAATGGTGGCGGGGTCAACTGTTGAACCACTAGCTCAGTTTGC
GACTGGAATGAGTATTGTAAGAGCTGCAGAAGTGTCAAGAACGCCAGCGAAAAACAACAGTAAATATCTATAAATTACAAGCTG
ATAGTTATAAATCGAAATTACTTCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAAGTATGCTAAACTTGGTGAC
AATGTAAAGGTTTGCAGGTGTACAGTTTAAACGTTATAAAGTCAAGACGGATATTTCTGTTGATGAATGAAAAAATTGACAAC
AGTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAATCTACCTCAAAAACTAATGCTCAAGGTTTGGTTCG
TCGATGCTCTGGATTCAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCTTCAAAACATTACCAAGCTTAT
GCTGTACCGTTTGTGTTGGAATTACCAGTTGCTAATCTACAGGTACAGGTTTCTTTCTGAAATTAATATTTACCTTAAAAACGT
TGTAAGTATGAACCAAAAAACAGATAAAGATGTTAAAAAATTAGGTGAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAAT
GGTTCTTGAAATCTACAATCCCTGCCAATTAGGTGACTATGAAAAATTTGAAATTAAGTATAAATTTGCAGATGGCTTGACTTAT
AAATCTGTTGAAAAATCAAGATTGGTTGAAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACCAACAGTTGATAACCA
AAATACATTAAAAATTACGTTTAAACAGAGAAAATTTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCTTGTTTAAAAATCAAG
ATGCTCTTGATAAAGCTACTGCAAAATACAGATGATGCGGCATTTTGGAAATTCAGTTGCATCAACTATTAATGAAAAAGCAGTT
TTAGGAAAAGCAATTGAAAAATCTTTGAACTTCAATATGACCATACTCTGTATAAAGCTGACAATCCAAAACCATCTAATCCTCC
AAGAAAACCAAGATTCTACTGGTGGGAAACGATTGTAAAGAAAGACTCAACAGAAAACAAAACACTAGGTGGTGGTGGTGGTGGT
ATTTGTTGGCTTCTGATGGGACAGCAGTAAATGGACAGATGCTCTTATTAAAGCGAATACTAATAAAACATATATTGCTGGAGAA
GCTGTTACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGGAGTTAAAGGTTTGGCTTATGCAGTTGATGCGAA
TGCAGAGGGTACAGCAGTAACTTACAAATTTAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGATAAAGAAATCGAGTTTA
CAGTATCAAAACATCTTATAATACAAACCAACTGACATCACGGTTGATAGTGCTGATGCAACACCTGATACAAATTTAAACAAAC
AAACGTCCTTCAATCCCTAATCTGTTGGTATTGGTACGGCTATCTTTGTGCTATCGGTGCTGCGGTGATGGCTTTTGTCTGTAA
GGGGATGAAGCGTCGTACAAAAGATAAC

SEQ ID NO: 2

MKLSKKLLFSAAILTMVAGSTVEPVAQFATGMSIVRAAEVSVQERPAKTTVNIYKLQADSYKSEITSNGGIENKDGEVINSYAKLGD
NVKGLQGVQFKRYKVKTDISVDELKLLTTVEAADAKVGTILEEGVSLPQKTNAGQLVVDALDSKSNVRVLYVEDLKNSPSNTTKAY
AVPFVLELPVANSTGTGFLSEINIYPKNVVTDEPKTKDKVKKLQDDAGYTIIGEEFKWFLKSTIPANLGDYEFKFEITDKFADGLTY
KSVGKIKIGSKTLNRDEHYTIDEPTVDNQNTLKITFKPEKFKEIAELLKGMTLVKNQDALDKATANTDDAAFLIIPVASTINEKAV

LGKAIENTFELQYDHTPDKADNPKNPPRKPEVHTGGKRFVKKDSTETQTLGGAEFDLLASDGTAVKWTDALIKANTKNKYIAGE
AVTGQPIKLSHTDGTFEIKGLAYAVDANAEBGTAVTYKLKETKAPBGYVIPDKIEFTVTSQTSYNTKPTDITVDSADATPDTIKNN
KRPSIPNTGGIGTAIFVAIGAAMFAVKGMRRTKDN

- 5 The nucleotide and amino acid sequences of GBS 91 in Ref. 3 are SEQ ID 8937 and SEQ ID 8938. These sequences are set forth below as SEQ ID NOS 3 and 4:

SEQ ID NO. 3

ATGAAAAAGGACAAAGTAAATGATACTAAGCAATCTTACTCTCTACGTAAATATAAAATTTGGTTTAGCATCAGTAATTTTGGGTC
10 ATTCATAATGGTCACAAGTCCTGTTTTGCGGATCAAACCTACATCGGTTCAAGTTAATAATCAGACAGGCACTAGTGTGGATGCTA
ATAATCTTCCAAATGAGACAAGTGCGTCAAGTGTGATTACTTCCAAATGATAGTGTTCAGCGCTCTGATAAAGTTGTAATAGT
CAAAATACGGCAACAAAGGACATTACTACTCTTTAGTAGAGACAAAGCCAAATGGTGGAACAAACATTACCTGAACAGGGAATTA
TGTTTATAGCAAGAAACCGAGGTGAAAAATACACCTTCAAATCAGCCCCAGTAGCTTTCTATGCAAGAAAGGTGATAAAGTTT
TCTATGACCAAGTATTTAATAAGATAATGTGAAATGGATTTTCATATAAGTCTTTTGTGGCGTACGTCGATACGCAGCTATTGAG
15 TCACTAGATCCATCAGGAGGTTTCAAGACTAAAGCACCTACTCTGTAAACAAATTCAGGAAGCAATAATCAAGAGAAAAATAGCAAC
GCAAGGAAATTATACATTTTTCATATAAGTAGAAGTAAAAATGAAGCTAAGGTAGCGAGTCCAACTCAATTTACATTGGACAAAG
GAGACAGAATTTTTCAGACCAATACTAACTATTGAAGGAAATCAGTGGTTATCTTATAAATCATTCAATGGTGTTCGTCGTTTT
GTTTTGCTAGGTAAAGCATCTTCAGTAGAAAAACTGAAGATAAAGAAAAAGTGTCTCCTCAACCAAGCCCGTATTTACTAAAAAC
TGGTAGACTGACTATTCTAACGAAACAACTACAGGTTTTGATATTTAATTACGAATATTAAAGATGATAACGGTATCGCTGCTG
20 TTAAGGTACCGGTTTGGACTGAACAGGAGGGCAAGATGATTTAAATGGTATACAGCTGTAACTACTGGGGATGGCAACTACAAA
GTAGCTGTATCATTTGCTGACCATAAGAATGAGAAGGGTCTTTATAATATTCTTTTATACCTACCAAGAAGCTAGTGGGACACTTGT
AGGTGTAAACAGGAACATAAGTGACAGTAGCTGGAACATAATCTTCTCAAGAACCTATTGAAAATGGTTTAGCAAGACTGGTGT
ATAATATTATCGGAAGTACTGAAGTAAAAATGAAGCTAAAAATCAAGTCAGACCAATTTACTTTAGAAAAAGGTGACAAAATA
AATTATGATCAAGTATGACAGCAGATGGTTACCAAGTGGATTCTTACAAATCTTATAGTGGTGTTCGTCGCTATATTCTCTGTGAA
25 AAAGCTAACTACAAGTAGTGAAGAAAGCGAAAGATGAGGCGACTAAACCGACTAGTTATCCCAACTTACCTAAAACAGGTACCTATA
CATTTACTAAAACGTGATGTAAGAGTCAACCTAAAGTATCAAGTCCAGTGAATTTAATTTTCAAAGGGTGAAAAAATACAT
TATGATCAAGTGTTAGTAGTAGATGGTCATCAGTGGATTTCATACAAGAGTTATTCGGGTATTCGTCGCTATATTGAAATT

SEQ ID NO. 4

MKKQGVNDTKQSYSLRKYKFLASVILGSFIMVTSFVFADQTTTSVQVNNQGTSTVDANNSSNETSASSVITSNNDSVQASDKVNS
30 QNTATKDIITPLVETKPMVEKTLPEQGNVYVSKETEVIKNTPSKSAFVAFYAKKGDVFDQVFNKDNVWISYKSCFVRRYAAIE
SLDPSSGSETKAPTPTVNSGNNQEKIATQGNVYFHSKVEVKNEAKVASPTQFTLDKGDRIFYDQILITIEGNQWLSYKSFNGVRRF
VLLGKASSVEKTEDKEKVSPQPQARITKTGRLTISNETTTGFDILITNKKDDNGIAAVKVPVWTEQGGQDDIKWYTAVTGDNVYK
VAVSFADHKNEKGLYNIHLYQEASGTLVGVGTGKTVVAGTNSSQEPFENGLAKTGVIYNIIGSTEVKNEAKISSQTQFTLEKGDKI
NYDQVLTADGYQWISYKSYSGVRRYIPVKLLTSSSEKAKDEATKPTSYPNLPKTGTYTFTKTVDVKSQPKVSSPVEFNFQKGEKIH
35 YDQVLVDVGHQWISYKSYSGIRRYIEI

- The nucleotide and amino acid sequences of GBS 104 in Ref. 3 are SEQ ID 8777 and SEQ ID 8778. These sequences are set forth below as SEQ ID NOS 5 and 6:

SEQ ID NO. 5

ATGAAAAAGAGACAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAAATCCATTTGGTATATTGGTACAAGG
40 TGAACCCCAAGATACCAATCAAGCACTTGGAAAAAGTAATTTGTTAAAAAAACCGGAGACAAATGCTACACCATTAGGCAAGCGACTT
TTGTGTTAAAAATGACAATGATAAGTCAGAAACAAGTCAGAAACGTAAGAGGGTCTTGAGAGAACCACTTTGAAACATAAAA
CCTGGAGACTACACATTTAAGAGAGAGAAACAGCACCAATTGGTTATAAAAAAACTGATAAAACCTGGAAAGTTAAAGTTGCAGATAA
45 CGGAGCAACAATAATCGAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAGAGTTTGAATGCCCAATATCCAAATCAGCTA
TTTATGAGGATACAAAAGAAAATTACCCATTAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAATCCAATA
AATGGAAGAGATGGTGAAGAGAGATTTGCTGAAGGTTGGTTATCAAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATA
TAAAATTGAATTAAGTGTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAACCACTAGATGTCGTTGTGCTATTAGATA
ATTCAAATAGTATGAATAATGAAAGAGCCAATAATTCTCAAAGAGCATTAAGAGCTGGGGAAGCAGTTGAAAAGCTGATTTGATAAA
50 ATTACATCAATAAAGACAATAGAGTAGCTCTGTGACATATGCCTCAACCATTTTGTGTTACTGAAGCGACCGTATCAAAGGG
AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATTATCATAAACTACTTTTACAGCAACTACACATAAATT
ACAGTTATTTAAATTTAAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAAATCCAAAGGAAGCGGAGCATATAAATGGG
GATCGCACGCTCTATCAATTTGGTGGACATTACTCAAAGAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAAAGTTCTAA
TGCTAGAAAAAACTTATTTTTCACGTAACCTGATGGTGTCCCTACGATGTCTTATGCCATAAATTTAATCCTTATATATACACAT
CTTACCAAAACCAAGTTAATTTCTTTTAAATAAATACCAATGATGATTATCAAGAGGATTCTCCTCAAGAGGATTCTTAAACGGAATCAAGTGTAT
55 GATTATCAAAATGAAAGGAGATGGAGAGAGTTTAAACTGTTTTCGGATAGAAAAGTTCTGTTACTGGAGGAACGACACAAGC
AGCTTATCGAGTACCGCAAAATCAACTCTCTGTAATGAGTAATGAGGATATGCAATTAATAGTGGATATATTTATCTCTATTGGA
GAGATTCAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTTCTGCAACGAAACAAATCAAACCTCATGGTGAGCCAACA
ACATTACTTTAATGGAATATAAGACCTAAAGGTTTACGATTTTACTGTTGGGATTGGTTAAACGGAATCAAGTGTGAGTGAAC
TCTCTTGAAGCTGAGAAATTTATGCAATCAATATCAAGTAAACAGAAAATTATACTAATGTTGATGATACAAATAAAATTTATG
60 ATGAGCTAAATAAATACTTTAAACAAATGTTGAGGAAAAACATTCTATTGTTGATGGAATGTGACTGATCCTATGGGAGAGATG
ATTGAATTTCAATTTAAAAAATGGTCAAAGTTTACACATGATGATTACGTTTTGGTTGGAATGATGGCAGTCAATTTAAAAAATGG
TGTGGCTCTTGGTGGACCAACAGTGATGGGGGAATTTTAAAGATGTTACAGTGACTTATGATAAGACATCTCAACCATCAAAA

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DSPKDDKHSFKTKTEFEELKAKHNI TYGKVVNDKI VFAHNYANNETVADIAAAMKDGYSSEAKNI SHGTHVAGI FVGN SKRPAINGLLLEGAAPN
 AQVLLMRI PDKIDSDFGEAYAKAITDAVN LGAKT INMSIGKTADSL TALNDKVKLAL KLA SEKGVA VVVAAGNEGAFMGDYSKPLSTNPDTGTVN
 SPAISED TSVASYESL KTI SEVVET IEGKLVKLPIVTSKPFDKGAYDVVYANYGAKKDFEGKDFKGKIALIERGGGLDFMTKITHATNAGVVG
 5 I VIFNDQEKRGNF L I PYREL PVG I I SKVDGERI KNTSSQLTFNQSFVVD SQGGRMLEQSSWGVTAEGA I KPDVTASGFEI YSSTYNNQYQTM SG
 TSMASPHVAGLMTMLQSHLA EKYKGMNLD SKKLLLELSKNILMSSATALYSEEDKAFYS PRQQGAGVVDAEKA I QAQYYITGNDGKAKINLKRMGDK
 FDIITVTIHLKVEGVKELYYQANVATEQVNVKGFAL KPQALLDTNWQKVLIRLDETQVRFT IDASQFSQKLKEQMANGYFLEGFVRFEAKDSNQEL
 MSI PFVGFNGDFANLQALETPIYKLSKGSFYYPKNDTTHKDQLEYNESAPFESNNYTALITQSASWGYVDYVKNNGGELELAPESPKRI ILGT FEN
 10 KVEDKTIHLLERDAANNPYFAISPKNKGNRDEITPQATFLRNVKD I SAQVLDQNGNVIWQSKVLP SYRKNFHNNPKQSDGHYRMDALQWSGLDKDG
 KVVADGFFTYRLRYTPVAEGANSQESDFKVQVSTKSPNLPSRAQFDETNRTL SLAMPKESYVPT YRLQLVL SHVVKDEEYGD ETSYHYFHIDQEG
 KVTLPKTVKIGESEVAVDPKALT LVVEDKAGNFATVKLSDLLNKAVVSEKENAIVISNSFKYFDNLKKEPMFISKKEKVNKNLEEI ILVKPQTTV
 TTQSLSKETITKSGNEKVL TSTNNSSRVAKI I SPKHNGDSVNHTLPSTSDRATNGLFVGT LALLSLLLYLKP KTKNNK

The nucleotide and amino acid sequences of GBS 173 in Ref. 3 are SEQ ID 8787 and SEQ ID 8788. These sequences are set forth below as SEQ ID NOS 9 and 10:

SEQ ID NO. 9

ATGAAACGTAAATAC TTTATTCTTAATACCGTGACGGTTTAAACGTTAGCTGCTGCAATGAATAC TAGCAGTATCTATGCTAATAGTACTGAGACA
 AGTGCTTCAGTAGTTCCTACTACAAATACTATCGTTCAAAC TAATGACAGTAATCCTACCGCAAAATTTGTATCAGAATCAGGACAATCTGTAATA
 GGTCAAGTAAACACGATAATCTGCGGCGCTTACAACAGTTGACACGCCTCATCATATTCAGCTCCAGATGCTTTAAACCAACTCAATCAAGT
 CCTGTGCTGAGAGTACTTCTACTAAGTTAACTGAAGAGACTTACAAACAAAAGATGGTCAAGATTTAGCCAAACATGGTGAGAAGTGGTCAAGTT
 20 ACTAGTGAGGAAC TCGTTAATATGGCATAACGATATTTATGCTAAAGAAAACCCATCTTTAATGCAAGTCACTACTACTAGACGCCAAGAGCTATT
 GAAGAGGCTAGAAAAC TAAAGATACCAATCAGCCGTTT TTAGGTGTTCCCTTGTAGTCAAGGGGTTAGGGCACAGTATTAAAGGTGGTGAAACC
 AATTAATGCTTGTATGCTAGTGGAGATGGAAAATTAGCACATTTGACAGATTTGACAGTATGCTCAAAAATATAAAGATTATTATTATTAGGACAA
 ACGAACTTTCCAGAGTATGGGTGGCGTAATATAACAGATTCTAAATTATACGGTCTAACGCATAATCCTTGGGATCTTGCTCATATGCTGGTGGC
 TCTTCTGTGTGAAGTGCAGCAGCCATTTGCTAGCGGAATGACGCCAATTTGCTAGCGGTAGTGATGCTGGTGGTCTATCCGTATTCATCTCTTGG
 25 ACGGCTTGGTAGGTTTAAACCAACAAGAGGATTGGTGAGTAATGAAAAGCCAGATTTCGTATAGTACAGCAGTTCATTTCATTTAAGTCA
 TCTAGAGACGCAGAAACATTATTAACCTTATCTAAAGAAAAGCGATCAAAACGCTAGTATCAGTTAATGATTAAATCTTTACCAATTGCTTACT
 TTGAAATCACCATTGGGAACAGAAGTTAGTCAAGATGCTAAAAACGCTTATTATGGACAACGTCACATTCTTAAGAAAACAGGATTCAAAGTAACA
 GAGATAGACTTACCAATTGATGGTAGAGCATTATGCGGTGATTATTCACCTTGGCTATTGGCATGGGAGGAGCTTTTCAACAATTGAAAAGAC
 TTAAGAAAACATGGTTTACTAAAGAACGCTTGTATCTTATTTGGGCGATTGATTTATTTATCAAAATTCAGATAAGGCTGAACCTTAAGAAA
 30 TCTATTTATGGAAGCCCAAAAACATATGGATGATTATCGTAAGGCAATGGAGAAGCTTCAAGCAATTTCTATTTTCTTATCGCCAACGACCGCA
 AGTTTAGCCCTCTAAATACAGATCCATATGTAACAGAGGAAGATAAAGAGCGGATTATATAATATGGAAAACCTTAGCCCAAGAAAGAAATTGCT
 CTCCTTAAATCGCCAGTGGGAGCTATGTTGCTAGAACCTTTTACACAAATGCTAATATGACAGGACTCCCGACTATCAGTATCCCGACTTAC
 TTATCTGATCTCGTTTATCCCATAGGACGATGTTAATGGCAGGTGCAAACTATGATATGTTAATTAATTTGCAACTTTCTTTGAAAACAT
 CATGGTTTAAATGGAAGCAAGAAATAAGAAATTAAGAACTATCAGGCTTATGAGGCTTAATACAGCCTACTAGCTTCTTCAAGCTCAT
 35 TCATCATTAGTAAATTTAGAAGAAATTCACAGTTACTCAAGTATCTATCTTAAAAAATGGATGAAATCGTCTGTTAAAAAATAACCATCCGTA
 ATGGCATATCAAAAAGCACTTCTCTAAAACAGGTGATACAGAATCAAGCTATCTCAGTTTATAGTAGTAACCTTTTATTAGCTTGTTTAGCTTT
 GTAACAAAAGAAATCAGAAAAGT

SEQ ID NO. 10

MKRKYFILNTVTLTAAAMNTSSIYANSTETSASVVPNTNTI VQTNDSNPTAKFVSESGQSVIGQVKPDNSAALTTVDTPHHISAPDALKTTQSS
 PVVESTSTKLTEFTYKQKQDGLANMVRSGQVTSEBLVN MAYDI IAKENPSLNAVITRRQBAI EEARLKDNTNQPF LGVPLLVKGLGHSIKGGET
 NNGLIYADGKISTFDSYVKKYKDLGFI ILGQTNFPEYGRWNITDSKLYGLTHNPWDLAHNAGGSSGSSAAAISGMPTPIASGSDAGGSIRIPSSW
 TGLVGLKPTRGLVSNKEDPSYSTAVHPLTKSSRDAETLITLYLKKSDQTLVSNLDLSLP IAYTLKSPMGTEVVSQDAKNAIMDNVTFLRKQGFV
 45 EIDLPIIDGRALMRDYSLAIGMGAFSTIEKDLKKGFTKEDVDPITWAVHVIYQNSDKAELKKSIMEAQKHMDDYRKAMEKLHKQFPFI LSPPTTA
 SLAPLNTDPYVTEEDKRAIYNMENLSQEERIALFNRQWPEMLRRPTFTQIANMTGLPAISIPTYLSEGLPIGTM LMAGANYDMVLIKFATFFEKH
 HGFNVKQRIIDKEVKPSTGLIQPTNSLFKAHSSLVNLEENSQVTQVSI SKKWKMSVKNKPSVMAYQKALPKGTDESSLSPVLVVTLLACFSF
 VTKKNQKS

The nucleotide and amino acid sequences of GBS 276 in Ref. 3 are SEQ ID 8941 and SEQ ID 8942. These sequences are set forth below as SEQ ID NOS 11 and 12:

SEQ ID NO. 11

TTGCGTAAAAACAAAAC TACCATTGATAAACTTGCCATTGCGCTTATATCTACGAGCATCTTGCTCAATGCACAATCAGACATTAAAGCAAAT
 ACTGTGACAGAAGACACTCTCTGCTACCGAACAAGCCGTAGAACCCCAACAACATAGCAGTTCTGAGGAATCAGGATCATCAAAGGAAACTAAA
 55 ACCTCACAACCTCTAGTGATGTAGGAGAAACAGTAGCAGATGACGCTAATGATCTAGCCCTCAAGCTCCTGCTAAAAC TGTGATACACGACA
 ACCTCAAAAGCGACTATTAGGGATTGAACGACCCCTTCATGTCAAAACCTGCGAGGAAAAGCAGGCAAGGGAGCTGGGACCGTTGTTGCAGTG
 ATTGATGCTGGTTTGTATGATAAAATCATGAAGCGTGGCGCTTAAAGACAAAACCTAAAGCACGTTACCAATCAAAAGAAAATCTTGAAAAGACTAAA
 AAAGAGCAGGTTATACCTATGGCGAGTGGGTCAATGATAAGGTTGCTTATTACCACGACTATAGTAAAGATGGTAAACGCTGTTGATCAAGAA
 CACGGCACACACGTGTGAGGATCTTGTGAGGAAATGCTCCATCTGAAGTAAAGAACCTTACCGCTAGAAAGGTGCGATGCCTGAGGCTCAATTG
 60 CTTTGTAGCTGTGCGAATTTGTAATGGACTAGCAGACTATGCTGCTAATCAGCTCAAGCTATCAGAGATGCTTCAACTTGGGAGCTCAAGGTG
 ATTAATATGAGCTTTGGTAATGTGCACTAGCTTAGCCCAACCTTCCAGACGAAACCAAAAAGCCCTTGTACTATGCCAATCAAAAGGTGTTAGC
 ATTTGTGACCTCAGCTGGTAATGATAGTAGCTTTGGGGGCAAGCCCGCTACCTCTAGCAGATCATCTGATTATGGGCTGGTTGGGACACCTGCA
 CGGCGAGATTCAACATGACAGTTGCTTCTTACAGCCGACATAACAGACCTCACTGAAACCTGCTACGGTCAAAACAGCAGCTCAAGATAAGAGAA
 ATGCCCTGTTATTTCAACAACCGTTTGTAGCCAAACAAGGCTTACGACTATGCTTATGCTAATCGTGGTACGAAAGAGGATGATTTAAGGATGTC
 GAAGGTAAGATTGCCCTTATTGAACGTGGCGATATTGATTTCAAGATAAGATTGCAACGCTAAAAAGCTGGTGTGTTAGGGTCTTGTATCTAT
 65 GACAAATCAAGACAAGGGCTTCCGATTGAATTTGCCAAATGTTGACAGATGCTGCGGCTTTATCAGTCGAAGAGACGGTCTCTATTAAAGAC
 AATCCCCCAAAAACCATTTACCTTCAATGCGACACCTAAGGTATTGCCAACAGCAAGTGGCACCAACTAAGCCGCTTCTCAAGCTGGGGTCTGACA
 GCTGACGGCAATATTAAACCGGATATTGACGACCCGGCCAAAGATATTGTCATCAGTGGCTAACAAACAGTATGCTCAAGCTCTGGAACATAGT
 ATGCTGCAACCTTGGTAGCGGATATCAGGACTGTGCAAAAGCAATATGACACAGATATCCTGATATGACACCATCAGAGCTCTGATTATTA
 GCTAAGAAAGTATTGATGAGCTCAGCAACTGCCCTATATGATGAAGATGAAAAGCTTATTTTCTCTCGCCAACAGGAGCAGGAGCAGTCTGAT

GCTAAAAAGCTTCAGCAGCAACGATGTATGTAACAGATAAGGACAATACCTCAAGCAAGGTTACCTGAACAATGTTTCTGATAAAATTTGAAGTA
 ACAGTAAACAGTTTCAACAACTCTGATAAACTCAAGAGTTGTATTACCAAGTAACTGTTCAACAGATAAAGTAGATGGAAAAACACTTTGCCCTTG
 GCTCCTAAAGCATTGTATGAGACATCATGGCAAAAAATCACAATTCAGGCCAATAGCAGCAAAACAGTCACCGTTCCAATCGATGCTAGTCGATT
 5 AGCAAGGACTTGCCTGCCAAATGAAAAATGGCTATTTCTTAGAAGGTTTGTTCGTTTCAACAAGATCCTACAAAAGAAGAGCTTATGAGCATT
 CCATATATTGGTTTCCGAGGTGATTTTGGCAATCTGTCAGCCTTAGAAAAACCAATCTATGATAGCAAAAGACGGTAGCAGCTACTATCATGAAGCA
 AATAGTGATGCCAAAGACCAATTAGATGGTGATGATTACAGTTTACGCTCTGAAAAATACTTTACAGCACTTACCACAGAGTCTAACCCATGG
 ACGATTATTAAAGCTGTCAAAGAAGGGGTTGAAAAATAGAGGATATCGAATCTTCAGAGATCACAGAAACCAATTTTTCAGGTTACTTTTGCAAAA
 CAAGACGATGATAGCCACTACTATATCCACCGTCACGCTAATGGCAAAACCATATGCTGCGATCTCTCCAAATGGGGACGGTAACAGAGATTATGTC
 10 CAATTCGAAGGTACTTTCTTGCGTAATGCTAAAAACCTTGTGGCTGAAGTCTTGGCAAAAGAAGGAAATGTTGTTTGGCAAGTAGGTAACCGAG
 CAAGTTGTTAAAACTACAACATGACTTGGCAAGCACACTTGGTTCAACCCGTTTGGAAAAACGCGTTGGGACGGTAAAGATAAAGACGGCAAA
 GTTGTGCTAACCGGAACCTACACCTATCGTGTTCGCTACACGCCGATTAGCTCAGGTGCAAAAGAACAACACACTGATTTTGTATGTTGATTGTAGAC
 AATACGACACTGAAGTCGCAACATCGGCAACATTCTCAACAGAAGATAGTCGTTTGACACTTGCATCTAAACCAAAAACAGCCAACCGGTTTAC
 15 CGTGAGCGTATTGCTTACACTTATATGGATGAGGATCTGCCAACACAGAGTATATTTCTCAAATGAAGATGGTACCTTTACTCTTCTCTGAAGAG
 GCTGAAACAATGGAAGCGCTACTGTTCCATTGAAATGTGAGACTTTACTTATGTTGTTGAAGATATGGCTGGTAACATCACTTATACACCAAGTG
 ACTAAGCTATTTGGAGGGCCACTTAATAAGCCAGAACAAGACGGTTTCAGATCAAGCACCAGACAAGAAACAGAAAGCTAAACAGAACAGACGGT
 TCAGGTCAACACCAGATAAAAAAAGAACTAAACCAGAAAAAGATAGTTTCAGGTCAACACCAGGTAAACTCTCAAAAAGGTCAATCTTCT
 CGTACTCTAGAGAAACGATCTTCTAAGCGTGTCTTAGCTACAAAAGCATCAACAAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT
 TTACATCTCTTAAGTTAGTTATGACCACTTTCTTCTTGGGA

SEQ ID NO. 12

MRKKQKLPFDKLAIALISTSILLNAQSDIKANTVTEDTPATEQAVEPPQPIAVSEERSSSKETKTSQTPSDVGETVADDANDLAPQ
 APAKTADTPATSKATIRDLNDP SHVKTLQEKAGKGAGTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGITYGEWVN
 DKVAYYHDYKDGKNAVDQEHGTHVSGNLAPSEMKEPYRLEGAMPEAQQLLLMRVEIVNGLADYARNYAQAIRDAVNGLGAKVIN
 25 MSFGNAALAYANLPDETCKAFDYAKSKGVSVTSAGNDSFSGGKPLPLADHPDYGVVGTTPAADSTLTVASYSYSPDKQLTETATVK
 TDDHQQDKEMPVISTNRFEPNKAIDYAYANRGTKEDDFDKDVBGKIALIERGDIIDFKDIANAKKAGAVGLIYDNQDKGFPIELPNV
 DQMPAAFISSRDGLLLKDNPKTITFNATPKVLPTASGTKLSRFSSWGLTADGNIKPDIAAPGQDILSSVANNKYAKLSGTSMSAP
 LVAGIMGLLQKQYETQYPMTPSERLDLAKKVLMSATALYDEDEKAYFSPRQQGAGAVDAKKAASAATMYVTDKNTSSKVLNNV
 SDKFEVTVTVHNKSDKPQELYYQVTVQTDKVDGKHFAALAPKALYETSWQKITIPANSSKQVTVPIDASRFSKDLLAQMKNGYFLEG
 30 FVRFKQDPTKBEELMSIPIYIGFRGDFGNLSALEKPIYDSKDGSSYYHEANSDAKDQLDGDGLQFYALKNNFTALTTESNPWTIIKAV
 KEGVENIEDIESSEITETIFAGTFAKQDDSHYIHRHANGKPYAISPNGDGNRDYVQFQGTFLRNAKNLVAEVLDEKGNVWVTS
 EVTEQVVKYNNNDLASTLGSTRFEKTRWDGDKDKGKVANGTYTYRVYTPISSGAKQHTDFDVIDNTTPEVATSATPSTEDSR
 LTLASKPKTSQPVYRERIAITYMDEDLPTTEYISPNEGDTFTLPEEAETMEGATVPLKMSDFTYVVEDMAGNIITYTPVKLLEGHS
 NKPEQDGSQAPDKKPEAKPEQDGSQTPDKKKEKPEKSSGQTPGKTPQKGQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT
 35 NRLHLLKLVMTTFFLG

The nucleotide and amino acid sequences of GBS 305 in Ref. 3 are SEQ ID 207 and SEQ ID 208. These sequences are set forth below as SEQ ID NOS 13 and 14:

SEQ ID NO. 13

ATGGGACGAGTAATGAAAAACAATAACAACATTGAAAATAAAAAAGTTTATAGTCCTTGGTTTAGCAGATCTGGAGAAGCTGCTGC
 40 ACGTTTGTAGCTAAGTTAGGAGCAATAGTGACAGTTAATGATGGCAAAACCAATTTGATGAAAAATCCAACAGCACAGTCTTTGTGTTGG
 AAGAGGGTATTAAGTGGTTTGTGGTAGTCATCCTTTAGAAATGTTAGATGAGGATTTTGTGTTACATGATTAAAAATCCAGGAATA
 CCTTATAACAATCCTATGGTCAAAAAAGCATTAGAAAAACAATCCCTGTTTGAAGTGAAGTTAGCATACTTAGTTTCAGA
 ATCTCAGCTAATAGGTATTAAGGCTCTAACCGGAAAAACGCAACGCAACGATGATTGCGAAGTCTTAAATGCTGGAGGTGAGA
 45 GAGGTTTGTAGCTGGGAATATCGGCTTTCTGCTAGTGAAGTTGTTTACGGCTGCGAATGATAAAGATACTCTAGTTATGGAATTA
 TCAAGTTTTCAGCTAATGGGAGTTAAGGAATTCGTCTCATATTGCAAGTAATTACTAATTTAATGCCAATCATTTAGATTATCA
 TGGGCTCTTTGAAGATTATGTTGCTGCAAAATGGAATATCCAAAATCAATGTCTTCATCTGATTTTTTGGTACTTAATTTTAATC
 AAGGTATTTCTAAAGAGTTAGCTAAACTACTAAAGCAACAATCGTTCTTTCTTACTACGGAAGAAAGTTGATGGTGCTTACGTA
 CAAGACAAGCAACTTTTCTATAAAGGGGAGAAATATTATGTCAGTAGATGACATTTGGTGTCCAGGAAGCCATAACGTAGAGAATGC
 50 TCTAGCAACTATTGCGGTTGCTAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAACTTTAAGCAATTTTGGAGGTGTTAAAC
 ACCGCTTGCAATCACTCGGTAAGGTTTCATGGTATTAGTTTCTATAACGACAGCAAGTCAACTAATATATTGGCAACTCAAAAAGCA
 TTATCTGGCTTTGATAATACTAAAGTTATCCTAATTGCAAGGAGTCTTGATCGCGGTAATGAGTTTGTATGAATTTGATACCGATAT
 CACTGGACTTAAACATATGGTTGTTTATAGGGGAATCGGCATCTCGAGTAAACGCTGCTGCACAAAAAGCAGGAGTAACCTATAGCG
 55 ATGCTTTAGATGTTAGAGATGCGGTACATAAAGCTTATGAGGTGGCACAACAGGGCGATGTTATCTTGCTAAGTCTGCAAAATGCA
 TCATGGGACATGTATAAGAATTTCAAGTCCGTGGTGTATGAATTCATTGATACCTTCGAAAGTCTTAGAGGAGAG

SEQ ID NO. 14

MGRVMKTTTTFENKKVLVLGLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCVSHPLELLEDDEFCYMIKNPGI
 PYNPNMVKALEKQIPVLTEVELAYLVSESQILIGITGSGNKTMTTMMIAEVLNAGGQORGLLAGNIGFPASVQVQAANDKDTLVMEL
 60 SSFQLMGVKEFRPHIAVITNLMPTHLDYHGSFEDYVAAKWNINQNMSSSDFLVLFNQGISKEAKTTKATVPFSTTEKVDGAYV
 QDKQLFYKGENIMSVDDIGVPGSHNVENALATIAVAKLAGISNQVIRETLSNFGVVKHRLQSLGKVHGISFYNDKSKTNILATQKA
 LSGFDNTKVILIAAGGLDRGNEFDELIPDITGLKHMVVLGESASRVKRAAQKAGVTYS DALDVRDAVHKAYEVAQQGDVILLSPAN
 SWDMYKNFEVRGDEFIDTFESLRGE

The nucleotide and amino acid sequences of GBS 313 are in Ref. 3 are SEQ ID 4089 and SEQ ID 4090. These sequences are set forth as SEQ ID NOS 15 and 16 below:

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTAACTAGTGGTGGTGACGCCCTGGTATGAACCGTGCTATCCGTGCAGTTGTTTCGTAAAGCAATTTCTGAAGGTATG
 GAAGTTTACCGCATCAACCAAGGTTACTATGGTATGGTGACAGGGGATATTTCCCTTTGGATGCTAATTCGTTGGGGATACATCAACCGTGGA
 GGAACGTTTTTACGTTACGACAGTTATCCTGAATTTGCTGAACCTTGAAGGTGAGCTTAAAGGGATTGAACAGCTTAAAAACACGGTATTGAAGGT
 5 GTAGTAGTTATCGGTGGTGGTCTTATCATGGTGCTATGCGTCTAAGTACGACAGGTTTCCAGCTGTTGGTTTGGCGGTACAATTGATAAC
 GATATCGTTGGCACTGACTATACTATTGGTTTGTACACAGCAGTTGCGACAGCAGTTGAGAATCTTGACCGTCTTCGTGATACATCAGCAAGTCAT
 AACCGTACTTTTGTGTTGAGGTTATGGGAAGAAATGCAGGAGATATCGCTCTTGGTCAGGTATCGCTGCAGGTGCAGATCAAAATTATTGTTCTCT
 GAAGAAGAGTTCAATATTGATGAAGTTGTCTCAAATGTTAGAGCTGGCTATGCAGCTGGTAAACATCACCAAATCATCGTCTTGCAGAAGGTGTT
 10 ATGAGTGGTGATGAGTTTGCAAAAAACAATGAAAGCAGCAGGAGACGATAGCGATCTTCGTGTGACGAATTTAGGACATCTGCTCCGTGGTGGTAGT
 CCGACGGCTCGTGATCGTGTCTTAGCATCTCGTATGGGAGCGTACGCTGTTCAATTGTTGAAAGAAGGTGCTGGTGGTTTAGCCGTTGGTGTCCAC
 AACGAAGAATGTTGAAAGTCCAATTTAGGTTTAGCAGAAGAAGGTGCTTTGTTAGCTTGACTGATGAAGGAAAAATCGTTGTTAATAATCCG
 CATAAAGCGGACCTTCGCTTGGCAGCACTTAATCGTGACCTTGCCAACCAAGTAGTAAA

SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYGMVTDIFPLDANSVGDITNRGGTFLRSARYPEFAELEGQLKGIEQLKHHGIEG
 VVVGDDGSYHGAMRLTEHGFPAVGLPGTIENDIVGTDYTI GFDTAVATAVENLDRLRDTSSHNRTFVVVVMGRNAGDIALWSGIAAGADQIIVP
 EEEFNIDEVVSNNVRAGYAAGKHHQIIVLAEGVMSGDEFKTMKAAGDDSLRVNLGHLRGGSPTRDRVLSRMGAYAVQLLEKRGGLAVGVH
 NEEMVESPIGLAEBEGALFSLTDEGKIVVNNPHKADLRALNRLANQSSK

The nucleotide and amino acid sequences of GBS 322 in Ref. 3 are SEQ ID 8539 and SEQ
 ID 8540. These sequences are set forth below as SEQ ID NOS 17 and 18:

SEQ ID NO. 17

ATGAATAAAAAGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTCAAGCACAAAGAAACAGATACGACGTGGACAGCA
 CGTACTGTTTCAGAGGTAAGGCTGATTTGGTAAAGCAAGACAATAATCATCATATACTGTGAAATATGGTGATACACTAAGCGTTATTTTCAGAA
 25 GCAATGTCAATGATATGAATGTCTTAGCAAAAAATAATCAATTCGAGATATCAATCTTATTATCTCTGAGACAACACTGCAGTAACTTACGAT
 CAGAAGAGTCATACCTGCCACTTCAATGAAAATAGAAAACAGCAACCAATGCTGGTCAAACAACAGCTACTGTGGATTGAAAACCAATCAA
 GTTCTGTTGTCAGACCAAAAAGTTTCTCTCAATACAAATTCGGAAGGTATGACACCAGAAGCAGCAACACGATTGTTTCGCAATGAAGACATAT
 TCTTCTGCCCGAGCTTTGAAATCAAAAGAAGTATTAGCACAAGAGCAAGCTGTAGTCAAGCAGCAGCTAATGAACAGGTATCACCAGCTCCTGTG
 30 AAGTCGATTACTTCAGAAAGTTCAGCAGCTAAAGAGGAAGTTAAACCAACTCAGACGTCAGTCAGTCAACCAACAGATCACCAGCTTCTGTT
 GCCGCTGAAACACCAGCTCCAGTAGCTAAAGTAGCACCCGGTAGAACTGTAGCAGCCCTAGAGTGGCAAGTGTAAAGTAGTCACTCCTAAAGTA
 GAAACTGGTGATCACCAGAGCATGTATCAGCTCCAGCAGTTCTGTGACTACGACTTCACCAGCTACAGACAGTAAGTTACAAGCGACTGAAGTT
 AAGAGCGTTCCGGTAGCACAAAAGCTCCAAACAGCAACACCCGGTAGCACAAACAGCTTCAACAACAATGCAGTAGCTGCACATCCTGAAAATGCA
 GGGCTCCAACCTCATGTTGCAGCTTATAAGAAAAAGTAGCGTCAACTTATGGAGTTAATGAATTCAGTACATACCGTGCCGGGAGATCCAGGTGAT
 35 CATGGTAAAGTTTAGCAGTTGACTTTATTGTAGTACTAATCAAGCACTTGGTAATAAAGTTGCACAGTACTCTACACAAAATATGGCAGCAAT
 AACATTGCTATGTATCTGGCAACAAAAGTTTACTCAATAAAGTAAACAGTAAATATTGGACCTGTCTAATCTTGAAGTGAATGCCAGATCGTGGT
 GGCCTTACTGCCAACCACTATGACCAGCTTCAGGTATCATTTAACAAATAATATAAAAAAGGAAGCTATTGGCTTCTTTTTATATGCCTTGAAT
 AGACTTTCAGGTTCTTATATAATTTTTATTA

SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETDTTWTARTVSEVKADLVKQDNKSSYTVKYGDITLSVI SEAMS IDMNVLAKINNIADINLIYPETTLTIVTYD
 40 QKSHATSMKIEPTPATNAAGQTTATVDLKTNQVSVADQKVS LNTISEGMTPEAATTVI VSPMKTYSSAPALKSKEVLAQEQAVSQAAANEQVSPAPV
 KSIITSEVPAAKEEVKPTQTSVQSSTTVSPASVAAETPAPVAKVAVVRTVAAPRVASVKVVTPKVVETGASPHVSPAPVPTTSPATDSKLQATEV
 KSPVPAQKAPTATPVAQPASTTNAVAHPENAGLQPHVAAYKEKVASTYGVNBFSTYRAGDPGDHKGGLAVDFIVGNTQALGNKVAQYSTQNMAAN
 45 NISYVIWQQKFYSNTNSIYGPAWTWNAMPDRGGVTANHYDHHVHSFNK

The nucleotide and amino acid sequences of GBS 328 in Ref. 3 are SEQ ID 6015 and SEQ
 ID 6016. These sequences are set forth below as SEQ ID NOS 19 and 20:

SEQ ID NO. 19

ATGAAAAAGAAAATATTTTGAAAAGTAGTGTTCTTGGTTTAGTCGCTGGGACTTCTATTATGTTCTCAAGCGTGTTTCGCGGACCAAGTCGGTGTC
 CAAGTTATAGGCGTCAATGACTTTCATGGTGCACCTTGACAATACTGGAACAGCAAATATGCCTGATGGAAGGTTGCTAATGCTGGTACTGCTGCT
 CAATTAGATGCTTATATGGATGACGCTCAAAAAGATTTCAAACAACTAACCCCTAATGGTGAAAGCATTAGGGTTCAAGCAGGCGATATGGTTGGA
 50 GCAAGTCCAGCCAACCTCTGGGCTTCTTCAAGATGAACCAACTGTCAAAAATTTTAAATGCAATGAATGTTGAGTATGGCAGATTGGGTAACCATGAA
 TTTGATGAAGGGTTGGCAGAATATAATCGTATCGTTACTGGTAAAGCCCTGCTCCAGATTCTAATATTAATAATATTACGAAATCATACCCACAT
 GAAGCTGCAAAACAAGAAATTTAGTGGCAAAATGTTATTGATAAAGTTAAACAAACAAATTCCTTACAATTGGAAGCCTTACGCTATTAAAAATATT
 55 CCTGTAAATAACAAAAGTGTGAACGTTGGCTTTATCGGGATTGTCAACAAAGACATCCCAAACCTTGTCTTACGTAAAAATATGAACAAATATGAA
 TTTTATAGTAAGCTGAAACAATCGTTAAATACGCCAAAGAATTACAAGCTAAAAATGTCAAAGCTATTGTAGTTCTCGCACATGTACCTGCAACA
 AGTAAAAATGATATTGCTGAAAGGTGAAGCAGCAAAATGATGAAAAGTCAATCAACTCTTCCCTGAAAATAGCGTAGATATTGCTCTTGTCTGGA
 CACAATCATCAATATACAAATGGTCTTGTGGTAAAACCTGATTTGTACAAGCGCTCTCTCAAGGAAAAGCCTATGCTGATGTACGTGGTGTCTTA
 60 GATACTGATACACAAGATTTCAATGAGACCCCTTCAGCTAAAGTAATTGCAGTTGCTCCTGGTAAAAAACAGGTAGTGCCGATATTCAAGCCATT
 GTTGACCAAGCTAATACTATCGTTAAACAAGTAACAGAAGCTAAAATTGGTACTGCCGAGGTAAGTGTCAATGATTACCGGTTCTGTTGATCAAGAT
 AATGTTAGTCCGCTAGGAGCCCTCATCACAGAGGCTCAACTAGCAATTGCTCGAAAAAGCTGGCCAGATATCGAATTTGGCCATGACAAATAATGGT
 GGCATTCTGTGCTGACTTACTCATCAACCAAGATGGAACAATCACCTGGGGAGCTGCACAAGCAGTTCAACCTTTTGGTAAATATCTTACAAGTCGTC
 65 GAAATTAATGTTAGAGATCTTTATAAAGCACTCAACGGAACAATACGACGAAAAACAAATTTCTTCTTCAAAATAGCTGGTCTGCGATACACTTAC
 ACAGATAATAAAGAGGGCGGGGAAGAAACACCATTTAAAGTTGTAAAAGCTTATAAATCAAAATGGTGAGGAAATCAATCTGTATGCAAAATACAAA
 TTAGTTATCAATGACTTTTATTTCGGTGGTGGTGGTGGCTTTGCAAGCTTCAGAAATGCCAACTTCTAGGAGCCATTAAACCCGATACAGAGGTA
 TTTATGGCCATATATCACTGATTAGAAAAGCTGGTAAAAAAGTGAGCGCTTCCAAATAATAAACCTAAATCTATGTCACTATGAAGATGGTTAAT
 GAACTATTACACAAAATGATGGTACACATAGCATTATTAAGAACTTTATTATGATCGACAAGGAAATATTGTAGCACAGAGATTGTATCAGAC

ACTTTAAACCAAAACAAAATCAAATCTACAAAATCAACCTGTAACTACAATTACAAAAACAATTACACCAATTTACAGCTATTAAACCTATG
AGAAATATGGCAAAACCATCAAACTCCACTACTGTAAAATCAAAATCAAAACCAAACTCTGAATATGGACAAATCATTCCTTATGTCTGTC
TTTGGTGTGGACTTATAGGAATTGCTTTAAATACAAAGAAAAACATATGAAA

5 SEQ ID NO. 20

MKKKI ILKSSVLGLVAGTSSIMFSSVFADQVGVQVIGVNDPHGALDNTGTANMPDGVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
ASPANSGLLQDEPTVKNFNAMNVEYGTILGNHEFDEGLAEYNRI VTGKAPAPDSNINNITKSYPHAAKQBI VVANVIDKVNKQI PYNWKPYAI KNI
PVMNKSVMVGFIVTKDI PNLVLRKNYEQYEFLEDEAETI VKYAKELQAKNVKAI VVLAHVPAATSKNDIAEGEAAEMMKVNLFPENSVDIVFAG
10 HNHQYTNGLVGKTRI VQALSQGKAYADVGVLDTDQDFIETPSAKVIAVAPGKKTGSADIQAI VDAQNTIVKQVTEAKI GTAEVSVMITRSVDQD
NVSPVGSLLITEAQLAIARKSWPDIDFAMTNNNGGIRADLLIKPDGTITWGAAQAVQPFGNILQVVEITGRDLYKALNEQYDQKQNFLLQIAGLRYTY
TDNKEGGEETPFKVVVKAYKSNNGEENPDAKYKLVINDFLFGGGDGFASFRNAKLLGAINPDTEVFMAIYITDLEKAGKKVSVPNKPKIYVVTMKNVN
ETITQNDGTHSI IKKLYLDRQGNIVAQEIVSDTLNQTQKSKSTKINPVTITHKQLHQFTAINPMRNYGKPSNSTTVKSKQLPKTNSEYQGSFLMSV
FGVGLIGIALNPKKKHMK

15 The nucleotide and amino acid sequences of GBS 330 in Ref. 3 are SEQ ID 8791 and SEQ
ID 8792. These sequences are set forth below as SEQ ID NOS 21 and 22:

SEQ ID NO. 21

ATGAATAAACCGCTAAAAATCGTTGCAACACTTGGTCTGCGGTGAATTCGTGGTGGTGAAGAAGTTTGGTGAGTCTGGATACTGGGGTGAAAGC
CTTGACGTAGAAAGCTTCAGCAGAAAAATTGCTCAATTGATTAAAGAAGGTGCTAACGTTTTCCGTTTTCAACTTCTCAGATGGAGATCATGCTGAG
20 CAAGGAGCTCGTATGGCTACTGTTTCGTAAAGCAGAGAGATTGACAGCAAAAAGTTGGCTTCTCCTTGATACTAAAGGACCTGAAATTCGTACA
GAACCTTTTGAAGATTGGTGAGATTTCATTCATATACAAACAGGTACAAAATTCGTGTTGCTACTAAGCAAGGTATCAAAATCAACTCCAGAAAGTG
ATTGCATTGAATGTTGCTGGTGGACTTGACATCTTTGATGACGTTGAAGTTGGTAAAGCAAAATCCTTGTGATGATGGTAAACTAGGTCTTACTGTG
TTTGCAAAAGATAAAGACACTCGTGAATTTGAAGTAGTTGTTGAGAAATGATGGCCTTATTGGTAAACAAAAGGTGTAACATCCCTTATACTAAA
25 ATTCCTTTCCAGCACTTGCAAGAACGCGATAATGCTGATATCCGTTTTGGACTTGAGCAAGGACTTAACCTTATTGCTATCTCATTTGTACGTACT
GCTAAAGATGTTAATGAAGTTGCTGCTATTGTTGAAGAACTGGSMATGGACACGTTAAGTTGTTTGCTAAAATTGAAAATCAACAGGTATCGAT
AATATTGATGAGATTATCGAAGCAGCAGATGGTATTATGATTGCTCGTGGTATATGGGTATCGAAGTTCCATTGAAATGGTTCCAGTTTACCAA
AAAATGATCATTACTAAAGTTAATGCAGCTGGTAAAGCAGTTATTACAGCAACAAATATGCTTGAAACAAATGACTGATAAACACAGTGGCGACTCGT
30 TCAGAAGTATCTGATGCTTCAATGCTGTTATTGATGGTACTGATGCTACAATGCTTTCAGGTGAGTCAGCTAATGGTAAATACCCAGTTGAGTCA
GTTTCGTACAATGGCTACTATTGATAAAAAATGCTCAACATTACTCAATGAGTATGGTTCGCTTAGACTCATCTGCATTCCCACGTAATAACAAAAT
GATGTTATTGCTATCTGCGGTAAAGATGCAACACACTCAATGGATATCAAACTTGTGTAACAATTACTGAAACAGGTAAATACAGCTCGTGCCATT
TCTAAATTCGCTCCAGATGCAGACATTTTGGCTGTTACATTTGATGAAAAGTACAACGTTTATTGATGATTAATCGGGGTGTTATCCCTGTCTCT
GCAGACAAACAGCATCTACAGATGATATGTTGAGGTTGCAGAACGTTAGCACCTTGAAGCAGGATTGTTGAATCAGGCGATAATATCGTTATC
GTTGCAGTGTTCTGTAGGTACAGGTGGAACATAACCAATGCGTGTTCGTACTGTTAAA

35 SEQ ID NO. 22

MNKRKVI VATLGPVAVEFRGGKKGESGYWGESLDVEASAEDIAQLIKEGANVFRFNFSHGDAEQGARMATVRKABEIIAGQKVGFLLDTKGPEIRT
ELFEDGADFHSYTTGTLRVATKQGIKSTPEVIALNVAGGLDIFDDVEVGKQILVDDGKGLGLTVFAKDKDTREFEVVENDGLIGKQKGVNIPYTK
IPFPALAEERDNADIRFLEQGLNFIAISFVRTAKDVNEVRAICBETGXGHVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVFPFEMPVYQ
40 KMIITKVNAAGKAVITATNMLETMDKPRATRSEVSDVFNVAVIDGTDATMLSGESANGKYPVESVRTMATIDKNAOTLLNEYGRLLDSAFPPRNKT
DVIASAVKDATHSMDIKLVVITITETGNTARAIKFRPDADILAVTFDEBKVQSRSLMINWGVIPVLADKPASTDDMFVAVALEAGFVESGDNIVI
VAGVPVGTGGTNTMRVRTVK

The nucleotide and amino acid sequences of GBS 338 in Ref. 3 are SEQ ID 8637 and SEQ
ID 8638. These sequences are set forth below as SEQ ID NOS 23 and 24:

45 SEQ ID NO. 23

TTGTCTGCTATAATAGACAAAAGGTGGTGATATTTATGTATTTAGCATTAAATCGGTGATATCATTAAATCAAAACAGATACTTGA
ACGTGAAACTTTCCAAAGCTCTTTTCAGCAACTAATGACCGAATCTCTGATGTATATGGTGAAGAGCTGATTTCTCCATTCACTA
TTACAGCTGGTGATGAATTTCAAGCTTTATTGAAACCATCAAAAAGGTATTTCAAATTATTGACCATATTCACTAGCTCTAAAA
50 CCTGTTAATGTAAGGTTTCGGCTCGGTACAGGAAACATTATAACATCCATCAATCAAAATGAAAGTATCGGTGCTGATGGTCTCTGC
CTACTGGCATGCTCGCTCAGCTATTAATCATATACATGATAAAATGATTATGGAACAGTTCAAGTAGCTATTTGCCTTGATGATG
AAGACCAAAACCTTGAATTAACACTAAATAGTCTCATTTTCAGCTGGTGATTTTATCAAGTCAAAATGGACTACAAACCATTTTCAA
ATGCTTGAGCACTTAATACCTTCAAGATAATTATCAAGAACAAATTTCAACATCAAAAGTTAGCCCACTGGAAAATATTGAACCTAG
TGCGCTGACTAAACGCCTTAAAGCAAGCGTCTGAAGATTTACTTAAGAACGAGAACACAGGCAGCCGCTATTAGTTAAAAGTT
55 GCACTCAAACTAAAGGGGGAAGCTATGATTTC

SEQ ID NO. 24

MSAIDKKVVI FMYLALIGDI INSKQILERETFQQSFQQLMTELSDVYGEELI SPFTITAGDEFQALLKPSKKVFIQI IDHIQLALKPVNVFRGLGTG
NIITSINSNESIGADGPAYWHARSA INHIHDKNYDGTQVQAI CLDDEQNLBELTLNLSI ISAGDFI KSKWTTNHFQMLEHLI LDQNYQEQQFQHKLAQ
60 LENIEPSALT KRLKASGLKI YLRTRTQAADLLVKSTCTQTKGGSYDF

The nucleotide and amino acid sequences of GBS 358 in Ref. 3 are SEQ ID 3183 and SEQ
ID 3184. These sequences are set forth below as SEQ ID NOS 25 and 26:

SEQ ID NO. 25

ATGTTTTATACAAATGAAGAGCTGGTAGAGCAAGCTAATAGCCAAACATAAGGGTAACATAGCAGAGCTCATGATCCAAACGGAAATTGAAATGACT
GGTAGAAGTCGTGAAGAAATTCGTTATATTATGTCCTCGAAATCTTGAAGTCATGAAAGCTTCGTATTGATGGATTAAACCCCTAGTAAATCAATC
AGTGGTTTAAACAGGCGGTGATGCTGTCAAGATGGATCAATATTTACAATCAGGAAAACTATTTAGATACCAATCCTAGCTGCCGTTAGGAAT
GCTATGGCTGTTAATGAGTTAAATGCTAAGATGGGACTGGTCTGTGCAACACCAACTGCAGGTAGTGCAGGATGTTTACCAGCTGTGATTCTTACA
GCCATTGAAAGCTTAATTTAACAGAAGAAGAGCAACTTGATTCTTATTTACAGCCGGCGCATTTGGTCTCGTCATTGGTAATAATGCCTCTATC
TCAGGTGCAGAAGGAGGTTGCCAAGCTGAAGTTGGGTGAGTGTGCTATGGCTGCGGCTGCTTTAGTTATGGCTGCTGGAGGTACTCCTTTCCAA
GCTAGCCAAGCTATAGCATTGTTTATTTAAAAATATGCTTGGACTTATCTGTGACCCTGTTCAGGTTTAGTTGAAGTCCCTTGTGTGAAGCGGAAT
GCTCTTGGATCAAGTTTTCGACTTGTGCTGCTGATATGGCCTTGGCTGGTATTGAATCGCAAATCCAGTAGTAAGTTATTGATGCAATGTAT
CAAGTTGGATCAAGTTTACCAGCTGCTTTTCGTGAGACTGCAGAAGGAGGACTTGTGCCACGCCGACAGGAAGCGTTATAGTAAAGAAATTTTT
GGGGAA

SEQ ID NO. 26

MFYTIIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGDDAVKMDQYLSQSKTISDTTILAAVRN
AMAVNELNAKMGLVCAFTPTAGSAGCLPAVISTAIEKLNLTBEEQLDFLTAGAFGLVIGNNASISGAEGGCQAEVGSASAMAAALVMAAGGTPFQ
ASQAIAFVKNMNLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSLSLPTAFRETAEGGLAATPTGRRYSKEIF
GE

The nucleotide and amino acid sequences of GBS 361 in Ref. 3 are SEQ ID 8769 and SEQ
ID 8770. These sequences are set forth below as SEQ ID NOS 27 and 28:

SEQ ID NO. 27

ATGAGCGTATATGTTAGTGAATAGGAATTATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTTCGACTTAAAGAAGGAATTT
CTAAACATTTATATAAAATCAGCACTCTATTTTGAATCTTATACAGGAAGCATACTAGTGACCCAGAGGTTCTCTGAGCAATCAAGATGAGAC
ACGTAATTTTAAATTTGCTTTTACCCTTTTGAAGAGGCTTCTGCTTCTTCAAGTGTTAAATTTAAAGCTTATCAATATTTGCTGTGTTTAGGG
ACCTCACTTGGGGGAAAGAGTCTGGTCAAAATGCCTTGTATCAATTTGAAGAAGGAGAGCGTCAAGTAGATGCTAGTTTATTAGAAAAAGCATCTG
TTTACCATATGCTGATGAATTGATGGCTTATCATGATATTGTGGGAGCTTCGTATGTTATTCAACCGCCTGTTCTGCAAGTAATAATGCCGTAAT
ATTAGGAACACAATTACTTCAAGATGGCGATTGTGATTTAGCTATTGTGGTGGCTGTGATGAGTTAAGTGAATATTCTTTAGCAGGCTTCAACATCA
CTAGGAGCTATTAAACAGAAATGGCATGTCAGCCCTATTCTTCTGAAAAGGAATCAATTTGGGTGAGGGCGCTGGTTTTGTGTTCTTGTCAAAG
ATCAGTCCCTTAGCTAAATATGAAAAATATCGGTGGTCTTATTACTTCAAGTGGTTATCATATAACAGCACCTAAGCCAAACAGGTGAAGGGGCGGC
ACAGATTGCAAAGCAGCTAGTGACTCAAGCAGGTATTGACTACAGTGAGATTGACTATATTAAACGGTCACGGTACAGGTACTCAAGCTAATGATAAA
ATGAAAAAAATATGATAGTAAAGTTTTCCTGACAAACGACATTGATCAGCAGTACCAAGGGGCAACCGGTCATCTAGGGGCTGCAGGTATTA
TCGAATTGATTAATGTTTAGCGGCAATAGAGGAACAGACTGTACAGCACTAAATAATGAGATTGGGATAGAAGTTTTCAGAAAAATTTGTCTA
TCATCAAAAGAGAGAATACCAATAAGAAATGCTTTAAATTTTTCGTTTGTCTTTGGTGGAATAATAGTGGTGTCTTATTGTCTCTTTAGATTCA
CCTCTAGAAACATTACCTGCTAGAGAAAAATCTTAAATGGCTATCTTATCATCTGTTGCTTCCATTTCTAAGAAATGAATCACTTTCTATAACCTATG
AAAAAGTTGCTAGTAATTTCAACGACTTTGAAGCATTACGCTTTAAAGGGGCTAGACCAACCCAAACTGTCAACCCAGCACAATTTAGGAAAAATGGA
TGATTTTCCAAAATGGTTGCCGTAACAACAGCTCAAGCACTAATAGAAAGCAATATTAACTTAAAAAACAAGATATCTTCAAAAGTAGGAATTGTA
TTTACAACACTTTCTGGACCAAGTTGAGGTTGTTGAAGGTATTGAAAAGCAAATCACAACAGAAGGATATGCACATGTTTCTGCTTCAAGATTCCCGT
TTACAGTAATGAATGCAGCAGCTGGTATGCTTTCTATCATTTTAAAAATAACAGGTCTTTTATCTGTCAATTCGACAAATAGTGGAGCGCTTGATGG
TATACAAATATGCCAAGAAATGATGCGTAACGATAATCTAGACTATGTGATTCTTGTCTTCTGCTAATCAGTGGACAGACATGAGTTTATGTGGTGG
CAACAAATTAACATATGATAGTCAAATGTTTGTGCGTTCTGATTATTGTTTCAAGCAAGTCTCTCTCGTCAAGCATTGGATAATTCTCCTATAATAT
TAGGTAGTAAACAAATTAATAATATAGCCATAAAACATTACAGATGTGATGACTATTTTGTATGCTGCGCTTCAAAATTTATATCAGACTTAGGACT
AACCATAAAGATATCAAGGTTTCTGTTTGAATGAGCGGAAGAGGCAAGTATTGATTCTTATGACGAACATTGTTCTGAGTATGATTAAT
ATGCCAAACCTTGCTTCTGGTCAAGTTTGGATTTCATCTAATGGTGTGCTGGTGAAGAACTGGACTATACTGTTAATGAAAGTATAGAAAAGGGCTATT
ATTTAGTCCCTATCTTATTCGATCTTCTGGTGGTATCTCTTTTGTCTATTATTGAAAAAAGG

SEQ ID NO. 28

MSVYVSGIGIISLGNKYSEHKQHLFDLKEGISKHLYKNHDSILESYSITSDPEVPEQYKDETRNFKFAFTAFEBALASSGVNLKAYHNIACVCLG
TSLGKSGAGQNALYQFEEGERQVDASLLEKASVYHIADELMAYHDIVGASYVISTACASNNAVILGTQLLDQDGLAI CGGCDLSLDSI SLAGFTS
LGAINTEMACQPVYSSGKGINLGBGAGFVVLVDQSLAKYGI IGGILITSDGYHITAPKPTGEGAAQIAKQLVTQAGIDYSEIDYINGHGTGTQANDK
MEKNMYGKFPTTTLLISSTKGQTGHTLGAAGI IELINCLAAIEEQVTPATKNEIGIEGFPENFVYHQKREYPI RNALNFSFAFGNNSGVLLSSLD
PLETLPAARENLMKMAILSSVASISKNESLSITYEKVANSFNDFEALRFKGPAPKPTVNPQFRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGIV
FTLLSGPVVEVIEKQITTEGYAHVSASRFPFTVMNAAAGMLSI IFKITGPLSVISTNSGALDGIQYAKEMMRNDNLGYVILVSNQWTDMSFMWW
QQLNYSQMFVGSYCSAQVLSRQALDNP IILGSKQLKYSHKTPDVTM I FDAALQNLSDGLTIKDI KGFVWNERKKAVSSDYDFLANLSEYYN
MPNLASGQGFSSNGAGEELDYTVNESIEKGYLLVLSYSIFGGISFAIEKR

The nucleotide and amino acid sequences of GBS 404 in Ref. 3 are SEQ ID 8799 and SEQ
ID 8800. These sequences are set forth below as SEQ ID NOS 29 and 30:

SEQ ID NO. 29

ATGAAAATAGATGACCTAAGAAAAAGCGACAATGTTGAAGATCGTCGCTCCAGTAGCGAGGTTCTATCTCTAGCGGAGGAAGTGGATTACCGATT
CTTCAACTTTTATGCTGCGAGGGAGTTGGA AAAACCAAGCTTGTGGTTTAAATCATCTTACTGCTACTTGGCGGAGGGGGACTAACCCAGCATTTT
AATGACTCATCTCCTCCTCTAGTTACCAATCTCAGAATGTCTCAGCTTCTGTTGATAATAGCGCAACGAGAGAACAAATCGATTTCGTTAATAAA
GTCTTGGCTCAACTGAGGATTCTGGTCAAGAATTTCCAAACCAAGGTTTGGAAATTATAAGGAACCAAACTGTCTTTACACCAATTCAT
ATTCAACAGGTTGTGGTATAGGTGAATCTGCTTCAGGACCATTTATTGTTTCAAGCAGATAAAAAATCTATCTTGATATTCTTTTACAATGAA
TTATCACATAAATATGGTGCTACTGGTGATTTCCTATGGCTACGTCATCGCCACGAAGTTGGTCACCACATTCAAACAGAGTTAGGCATTATG
GATAAGTATAATAGAATGCGACACGGACTTACTAAGAAAGAAGCAATGCTTTAAATGTTTCGGCTAGAACTTCAAGCAGATTATTATGCAAGGGTA
TGGGCTCACTACATCAGGGGAAAAATCTCTTAGAACAAGGAGACTTTGAAGAGGCCATGAATGCTGCCACGCCGCTCGGAGACGATACCCCTCAG
AAAGAAACCTACGGAAAAATTAGTGCCTGATAGCTTTACCCATGGAACAGCTGAACAACGCCAAGCTTGGTTTAAACAAAGGCTTTCAATATGGTGAC
ATCCAACACGGTGTACTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

5 MKIDDLRKSNDVEDRRSSSGGSFSSGGSGLPILQLLLLRGSKTKLVLIILLLGGGLTSIFNDSSSPSSYQSQNVSRSDNSATREQIDFVNK
VLGSTEDFWSQEFQTOGFGNYKEPKLVLYTNSIQTCGIGESASGPFYCSADKKIYLDISFYNELSHKYGATGDFAMAYVIAHEVGHIIQTELGIM
DKYNRMHRHGLTKKEANALNVRLLEQADYYAGVWAHYIRGKNLLEQGFEEAMNAAHAVGDDTLQKETYGKLVPSFTHTGTAEQRQRWFNKGFGYGD
IQHGDTSVEHL

The nucleotide and amino acid sequences of GBS 656 in Ref. 3 are SEQ ID 9323 and SEQ
ID 9324. These sequences are set forth below as SEQ ID NOS 31 and 32:

SEQ ID NO. 31

10 ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAACGTA
ACGCCGATAGTACATGCTGATGTCAATTCATCTGTTGATACGAGCCAGGAATTTCAAATAATTTAAAAATGCTTGGTAACTTACCATTTCAA
TATGTTAATGGTATTATGAATTAATAATAATCAGACAAATTTAAATGCTGATGTCAATGTAAAGCGTATGTTCAAATAACAATTGACAATCAA
15 CAAAGACTATCACTGCTAATGCAATGCTTGATAGAACCATTCGTCAATATCAAATCGCAGAGATACCCTCTTCCCGATGCAAAATGGAAACCA
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTATGGACATGCAGTCGACAAGGGGCATTAAATGCTTATGCTTGGTAAATTTCAAAGGT
TGGGATGCTTCCGTGTCAAATCCTCAAATGTTGTCACACAAACAGCTCATTCACCAATCAAATCAAAAAATCAATCGTGGACAAAATTATTAT
GAAAGCTTAGTTGTAAGGCGGTTGACCAAAACAAACGTTGCTTACCGTGTAACTCCATGTACCGTAATGATACTGATTTAGTTCATTGCA
ATGCACCTAGAACTAATCACAAGATGGCACATTAGAAATTAATGTTGCTATTCCAACACACAAGCATCATACACTATGGATTATGCAACAGGA
GAAATAACACTAAAT

SEQ ID NO. 32

20 MKRLHKLFIITVIATLGLMGLVMTFGLPTQPQNVTPIVHADVNSSVDSQEFQNNLKNAIGNLPFYVNGIYELNNQTNLNADVNKAYVQNTIDNQ
QRLSTANAMLDRTIRQQRNRDITLTDANWKPLGWHQVATNDHYGHAVDKGHLIAYALAGNFKGWDASVSNPQNVVTTQTAHSNQSNOQKINRGQNY
ESLVRKAVDQNKVRVRYRVTPLYRNDTDLVPFAMHLEAKSQDGLBENVAIPNTQASYTMDYATGETTLN

25 The nucleotide and amino acid sequences of GBS 690 in Ref. 3 are SEQ ID 9965 and SEQ
ID 9966. These sequences are set forth as SEQ ID NOS 33 and 34 below:

SEQ ID NO. 33

30 ATGAGTAAACGACAAAATTTAGGAATTAGTAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATTGTAGTAATAGGTGGCTTTTTATGG
GTACAATCTCACTAATAAGAGTGCAAGTAAAACTAATACAAAGTTTAAATGTTAGAGAAGGAAGTGTTCGTCCTCACTCTTTTGACAGGA
AAAGCTAAGGCTAATCAAGAACAGTATGTGATTTTGTATGCTAATAAAGGTAATCGAGCACTGTCAAGTTAAAGTGGGTGATAAAATCACAGCT
GGTCAGCAGTTAGTTCATATGATACAACAAGTGCACAAGCAGCCTACGACACTGCTAATCGTCAATTAATAAAGTAGCGCGTCAGATTATAAT
CTAAAGACAACAGGAAGTCTTCCAGCTATGGAATCAAGTGATCAATCTTCTTCATCATCAAGGACAAGGGAAGTCAATCGACTAGTGGTGGCAGC
AATCGTCTACAGCAAAAATATCAAAGTCAAGCTAATGCTTCATACAACCAACAACCTTCAAGATTTGAATGATGCTTATGCGATGCAAGGCAGAA
35 GTAAATAAAGCACAAAAGCATTGAATGATACTGTTATTACAAGTGACGTATCAGGGACAGTTGTTGAAGTTAATAGTGATATTGATCCAGCTTCA
AAAAGTATGCAAGTACTTGTCCATGTAGCAACTGAAGGTAAACTTCAAGTACAAGGAACGATGAGTGAGTATGATTTGGCTAATGTTAAAAAGAC
CAGGCTGTTAAATAAAAATCTAAGGCTATCCTGACAAGGAATGGGAAGGTAAAAATTCATATATCTCAAAATTAACAGAGCAGAAACAAAC
AATGACTCTAATAACGGCTCTAGTGTCTGTAATATAAATATAAAGTAGATATTACTAGCCCTCTCGATGCATTAAACAAAGGTTTACCGTATCA
GTTGAAGTAGTTAATGAGATAAGCACCTTATTGTCCTTACAAGTTCTGTGATAAACAAGATAATAAACACTTTGTTTGGGTATACAATGATTCT
AATCGTAAATTTTCCAAGTTGAAGTCAAATTTGGTAAAGCTGATGCTAAGACACAAGAAATTTTATCAGGTTTGAAGCAGGACAAATCGTGGTT
40 ACTAATCCAAGTAAACCTTCAAGGATGGGCAAAAATTTGATAATATTGAATCAATCGATCTTAACCTAATAAGAAATCAGAGGTGAAA

SEQ ID NO. 34

45 MSKRQNLGISKKGAIISGLSVALIVVIGGFLWVQSQPNKSAVKNTYKVFNVREGSVSSSTLLTGKAKANQEQYVYFDANKGNRATVTVKVGDKITAG
QQLVQYDTTAAQAYDNTANRQLNKVARQINNLKTTGSLPAMESDQSSSSSQGGTQSTSGATNRLQQNYQSQANASYNQLQLNDAYADAQAEVN
KAQKALNDTVITSEVSGTVVEVNSDIDPASKTSQVLVHVATEGKLQVQGTMSYEDLANVKDQAVKISKVYPDKWEWEGKISYISNYPEAEANNDS
NNGSSAVNKKYKVDITSPLDALKQGFVSVSEVVNGDKHLIVPTSSVINKDNKHFVWVYVNDNSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVINPS
KTFKDGQKIDNIBSIDNSNNKKSEVK

The nucleotide and amino acid sequences of GBS 691 in Ref. 3 are SEQ ID 3691 and SEQ
ID 3692. These sequences are set forth as SEQ ID NOS 35 and 36 below:

SEQ ID NO. 35

55 ATGAAAAAATTGGAATTATTGTCCTCACACTACTGACCTTCTTTTGGTATCTTGGCGACAACAACTAAACAAGAAAGCACTAAAACACTATT
TCTAAATGCCTAAAATTGAAGGCTTCACTTATTGGAATAATTCCTGAAAAATCCGAAAAAGTAATTAATTTTACATATTCTTACACTGGGTAT
TTATTAATACTAGGTGTTAATGTTTCAAGTTACAGTTTAGACTTAGAAAAAGATAGCCCCGTTTGGTAAACAAGTAAAGAAAGCTAAAAATTA
ACTGCTGATGATACAGAACTTATGCGCGACAAAAACCTGATTTAATCATGTTTTCGATCAAGATCCAAACATCAATACTCTGAAAAAATTGCA
CCAACCTTAGTTATTAATATGGTGCAAAAATTTTAGATATGATGCCAGCCTTGGGGAAGTATTCGTTAAAGAAAAAGAAAGCTAATCAGTGG
GTTAGCCAATGAAAACTTAAACTCTCGCTGTCAAAAAGATTACACCATATCTTAAAGCCTAACACTACTTTTACTATTATGGATTTTATGAT
AAAAATATCTATTATAGGTAATAATTTTGGACGCGGTGGAGAACTAATCTATGATTCACTAGGTTATGCTGCCCGCAAAAAAGTCAAAAAAGAT
60 GTCTTTAAAAAGGGTGGTTTACCGTTTCGCAAGAAAGCAATCGGTGATTACGTTGGAGATTATGCCCTTGTTAATATAACAAACGACTAAAAAA
GCAGCTTCATCACTTAAAGAAAGTGATGTCTGGAAGAATTTACAGCTGTCAAAAAGGGGCACATCATAGAAAGTAACACGCTGTTTATTTCT
TCTGACCTCTATCTTTAGAGCTCAATTAAAAATCATTACAAAGGCTATCAAGAAAAATACAAAT

SEQ ID NO. 36

MKKIGIIVLTLLTFFLVSCGQQTQKQESTKTTISKMPKIEGFTYYGKIPENPKKVINFTYSYTGYYLLKLGVNVSSYSLDLEKDSVPV
GKQLKEAKKLTADDTEAIAAQKPDLMVFDQDPNINTLKKIAPTLVIKYGAQNYLDMMPALGKVFVGKEKEANQWVSQWKTTLAVK
KDLHHLLKPNNTTFTMDFYDKNIYLYGNFGRGGELIYDSLGYAAPEKVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKTTKKA
SSLKESDVWKNLPAVKKGHIIESNYDVIFYSDPLSLEAQLKSFTKAIENTN

Other preferred polypeptide antigens include: GBS4 (SEQ ID 2 from Ref. 3); GBS22 (SEQ ID 8584 from Ref. 3); and GBS85 (SEQ ID 216 from Ref. 3), including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The polypeptide is preferably not a C protein (alpha or beta or epsilon) or a R protein (Rib).

The nucleotide and amino acid sequences of GBS 4 in Ref. 3 are SEQ ID 1 and SEQ ID 2.

These sequences are set forth below as SEQ ID NOS 37 and 38:

SEQ ID NO. 37

ATGAAAGTGAAAAATAAGATTTTAACGATGGTAGCACTTACTGTCTTAACATGTGCTACTTATTCATCAATCGGTTATGCTGATCAAGTGATAAGA
ATACTGACACGAGTGTCTGACTACGACCTTATCTGAGGAGAAAAAGATCAGATGAACTAGACCAGTCTAGTACTGGTTCTTCTTCTGAAAAATGAATC
GAGTTCATCAAGTGAACAGAAACAAATCCGTCACTAATCCACCTACAACAGAACCATCGCAACCTCAGCTAGTGAAGAGAACAGCTGATGGT
AGAACGAAGACAGAAATTGGCAATAATAAGGATATTTCTAGTGAACAAAAGTATTAATTTTCAAGATAGTATTAAGAAATTTTAGTAAAGCAAGTA
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAGCAAAATGATGGGAAAAAAGGCCACAGTAAGCCTAAAAAGGAACCTCCTAAAC
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGATTATCTGTTATCATTAAAGTTTTTACAATAAGAAAATGAACTTTAT

SEQ ID NO. 38

MKVKNKILTMVALTVLTCATYSSIGYADTSDKNTDTSVVTTTSEEKRSDELQSSSTGSSSENESSSSSEPETNPSTNPPTTEPSQPSSEENKPDG
RTKTEIGNNKDISSGKTVLISEDSIKNFSKASSDQEEVDRESSSSSKANDGKKGHSKPKKELPKTGDSHSDTVIASTGGIILLSLSFYNKMKLY

The nucleotide and amino acid sequences of GBS 22 in Ref. 3 are SEQ 8583 and SEQ ID 8584. These sequences are set forth below as SEQ ID NOS 39 and 40:

SEQ ID NO. 39

ATGAAAGGATACGGAAGCCCTTATTTTTGTTCTCGGAGTAGTTACCTTAATTTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAATGGCT
TGTCAGTAGTGACTAGCTTTTATCCAGTATATTCATTACAAAAGCAGTTTCTGGTGATTGAATGATATTAATATGATTCGATCACAGTCAGGTAT
TCATGGTTTTGAACCTCATCAAGTATGTTGCTGCCATTATGATGCTGATCTATTCTTATCATTCGCACACACTAGAAGCTTGGGCGAGACGT
TTGGAACCTAGTTTGCATCACTCTAAGATATCTGTAATTGAAGCTTCAAAGGTATGACTTTGGATAAAGTTTATGGCTTAGAAGATGTAGAGGCAG
AAAAAGGAGTAGATGAGTCAACCTTGTATGACCCTCACACTTGAATGACCCTGTAAAGTATCTGAGGAAGCACAACTCATCGCTACACAATTAGC
TAAAAAGGATCCTAAAAACGCTAAGGTTTATCAAAAAATGCTGATCAATTTAGTGACAAGGCAATGGCTATTGCAGAGAAGTATAAGCCAAAATTT
AAAGCTGCAAAAGTCTAAATACTTTTGACTTCACATACAGCATCTCATACCTTAGCTAAGCGATACGGATTGACTCAGTTAGGTATTGCAAGGTGCTC
CAACCGAGCAAGAACCTAGTGCTAAAAAATTAGCCGAAATTCAGGAGTTTGTGAAAACATATAAGGTTAAGACTATTTTTGTTGAAGAAGGAGTCTC
ACCTAAATTAGCTCAAGCAGTAGCTTCAGCTACTCGAGTTAAATTTCAAGTTTAAAGTCTTTTARAAGCAGTTCCCAAAAACAATAAAGATTACTTA
GAAATTTGGAACTAATCTTAAGGTACTTGTCAATCGTTAAATCAATAG

SEQ ID NO. 40

MKRIRKSLIFVLGVVTLICLCACTKQSQQKNGLSVVTSFYFVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAAIYDADLFLYHSHTLEAWARR
LEPSLHHSKVSVEIASKGMLTDKVGLEDVEAEKGVDESTLYDPHTWNPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSDKAMATAEKYKPKF
KAASKYFVTSHTAFSLAKRYGLTQLGIAGVSTEQEPSAKKLAEIQEFVKTYKVKITFVEBGSVKLAQAVASATRVKIASLSPLXAVPKNNKDY
ENLETNLKVLVKSINQ

The nucleotide and amino acid sequences of GBS 85 in Ref. 3 are SEQ ID 215 and SEQ ID 216. These sequences are set forth below as SEQ ID NOS 41 and 42:

SEQ ID NO. 41

ATGCCTAAGAAGAAATCAGATACCCAGAAAAAGAAAGTGTCTTAACGGAATGGCAAAAGCGTAACCTTGAATTTTTAAAAAACGCAAGAAAG
ATGAAGAAGAACAAAAATCGTATTAAACGAAAAATACGCTTAGATAAAAGAAAGTAAATTAATATTCTTCTCCTGAAGAACCTCAAAATACTACTAA
AATTAAGAAGCTTCATTTTCCAAAGATTTCAAGACCTAAGATTGAAAGAAACAGAAAAAGAAAAATAGTCAACAGCTTAGCCAAACTAATCGC
ATTAGAAGCTGCACCTATATTTAGTAGCATTCTAGTCATTTTAGTTTCCGTTTTCTACTAATCCTTTTAGTAAGCAAAAAACAATAACAGTTA
GTGAAATCAGCATACACCTGATGATATTTGATAGAGAAAAACGAATATTCAAAAAACGATTAATTTCTTTCTTTAAATTTTAAACATAAAGCTAT
TGAACAACGTTTAGCTGCAGAAGATGTATGGGTAAAAACAGCTCAGATGACTTATCAATTTCCCAATAAGTTTTCATATTCAAGTTCAAGAAATAAG
ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGGAAACTGGAAAAAAGGCTGATCCTGTAAATAGTTTCAAGACTACCAAGCACT
TCTTAACATTAACCTTGATAAGGAAGATAGTATTAAGCTATTAATTAAGATTAAAGGCTTTAGACCCCTGATTAAATAGTGAGATTCAAGTGAT
AAGTTTAGCTGATTCTAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGGAAATAGTATTAGAATACCATTTCTAAATTTAAAGAAAGA
CTTCTTTTTTACAAACAAATTAAGAAGAACCTTAAGGAACCTTCTATTGTTGATATGGAAGTGGGAGTTTACACAAACAAACAAATACCATTTGAATCAA
CCCTGTTAAAGCAGAGATACAAAAATAAATCAACTGATAAAACACAAACACAAATGCTCAGGTTGCGGAAATAGTCAAGGACAAACAAATAA
CTCAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCTCAAATGTTAAT

SEQ ID NO. 42

MPKKKSDTPEKEEVVLTEWQKRNLEFLKKRKEDEEEQKRINEKLRLDKRSKLNISSEPEPQNTTKIKKLHFPKISRPKIEKKQKKEKIVNSLAKTNR
 IRTAPIFVVAFLVILVSVLLTPFSKQKTI TVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIBQRLAEDVWVKTAQMTYQFPNKFHIQVOENK
 I IAYAHTKQGYQPVLETGKKADPVNSSELPHFLTINLDKEDSIKLLIKDLKALDPLISEIQVLSLADSKTTTDLILLDMHDGNSIRIPLSKFKER
 LPFYKQIKKLNKEPSIVDMEVGVT'TTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGTNNSTNQGGQQTATEQAPNPQNVN

GBS polypeptides of the invention may be present in the composition as individual separate polypeptides. It is preferred, however, that two or more (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) of the antigens are expressed as a single polypeptide chain (a 'hybrid' polypeptide). Hybrid polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable hybrid partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

The hybrid polypeptide may comprise two or more polypeptide sequences from the first antigen group. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS antigen or a fragment thereof. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise different epitopes.

The hybrid polypeptide may comprise one or more polypeptide sequences from different GBS serotypes. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence selected from a GBS serotype selected from the group consisting of serotypes Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII. The first and second amino acid sequence may be from the same GBS serotype or they may be from different GBS serotypes. Preferably, the first and second amino acid sequence are selected a GBS serotype selected from the group consisting of serotypes II and V. Most preferably, at least one of the first and second amino acid sequences is from GBS serotype V. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference epitopes.

In one embodiment, the hybrid polypeptide comprises one or more GBS antigens from serotype V. Preferably, the hybrid polypeptide comprises a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence comprising a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the GBS antigen or fragment thereof is selected from the group consisting of GBS 80 and GBS 691. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference epitopes.

Hybrids consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

5 Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Preferably, the GBS antigen in one of the hybrid polypeptides is GBS 80 or a fragment thereof. Accordingly, examples of two-antigen hybrids for use in the invention may comprise: (1) 10 GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691. 15 Preferably, a two-antigen hybrid for use in the invention comprises GBS 80 and GBS 691.

Hybrid polypeptides can be represented by the formula $\text{NH}_2\text{-A-}\{-\text{X-L-}\}_n\text{-B-COOH}$, wherein: X is an amino acid sequence of a GBS antigen or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

20 If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of $X_2 \dots X_n$ will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

25 For each n instances of $\{-\text{X-L-}\}$, linker amino acid sequence -L- may be present or absent. For instance, when $n=2$ the hybrid may be $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-L}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-X}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-COOH}$, $\text{NH}_2\text{-X}_1\text{-X}_2\text{-L}_2\text{-COOH}$, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* 30 comprising Gly_n where $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$ or more), and histidine tags (*i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID 1), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the $(\text{Gly})_4$ tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags *i.e.* His_n where *n* = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X₁ lacks its own N-terminus methionine, -A- is preferably an oligopeptide (e.g. with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags *i.e.* His_n where *n* = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, *n* is 2 or 3.

The saccharide antigen

The saccharide antigen is generally the capsular polysaccharide of a GBS or a derivative thereof. Suitable derivatives include oligosaccharide (e.g. from 3 to 150, preferably 8 to 100, monosaccharide units) fragments of the polysaccharide (e.g. refs. 12 to 16), de-acetylated saccharides (Ref. 16), N-acroylated saccharides (16), saccharides with terminal aldehyde groups, *etc.*

The saccharide is preferably conjugated to a carrier molecule to enhance immunogenicity (e.g. see refs. 4 to 23 *etc.*). In some embodiments of the invention the GBS saccharide is conjugated to a GBS protein as defined above, thereby giving a polypeptide/saccharide combination of the invention in a single molecule. In other embodiments the GBS saccharide is conjugated to a non-GBS protein, in which case the conjugate will be combined with a separate GBS protein to give a polypeptide/saccharide combination of the invention.

Non-GBS carrier polypeptides include tetanus toxoid, the *N.meningitidis* outer membrane protein (24), synthetic peptides (25, 26), heat shock proteins (27, 28), pertussis proteins (29, 30), protein D from *H.influenzae* (31), cytokines (32), lymphokines (32), hormones (32), growth factors (32), toxin A or B from *C.difficile* (33), iron-uptake proteins (34) *etc.* Preferred carrier proteins are the CRM197 diphtheria toxoid (35) and tetanus toxoid.

The saccharide and polypeptide are joined covalently. This may involve a direct covalent bond between the saccharide and polypeptide, or indirect coupling via a linker or spacer may be used (e.g. via a B-propionamido linker (16), *etc.*). Any suitable conjugation chemistry may be used (e.g. reductive amination (21) *etc.*). Linkage is preferably via a terminal saccharide in the polysaccharide.

A single carrier molecule may carry saccharide antigens of a single type (*e.g.* saccharides derived from a single GBS serotype) or may carry multiple different antigens (*e.g.* saccharides derived from multiple GBS serotypes, all conjugated to the same carrier).

The saccharides can, of course, be prepared by various means (*e.g.* purification of the saccharide from GBS, chemical synthesis, *etc.*), in various sizes (*e.g.* full-length, fragmented, *etc.*) and may be derivatised for linking to carriers. They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal saccharides) or substantially isolated form. Processes for preparing capsular polysaccharides from GBS are well known in the art (*e.g.* refs. 36 to 39) and processes for preparing oligosaccharides from polysaccharides are also known (*e.g.* hydrolysis, sonication, enzymatic treatment, treatment with a base followed by nitrosation, *etc.* (12 to 16)).

As an alternative to using a saccharide antigen in non-conjugated combinations, a peptide mimetic of the GBS capsular polysaccharide may be used (*e.g.* 40). Suitable peptides can be selected by techniques such as phage display using protective anti-saccharide antibodies. As a further alternative, an anti-idiotypic antibody may be used instead of a saccharide antigen (*e.g.* ref. 41).

Prime/boost schedules

Polypeptide/saccharide combinations of the invention may be given as single doses or as part of a prime/boost schedule. In a prime/boost schedule, the combinations may be used as the priming dose, the boosting dose(s), or both.

If a combination is used for both priming and boosting, it is preferred to use the same combination both times. If a combination is used for only one of priming and boosting, it is preferred that the other dose should use the polypeptide or saccharide on which the combination is based. Thus the invention provides a prime-boost schedule where either (i) one of the saccharide and polypeptide antigens is used for priming an immune response and a combination are used for boosting the response, or (ii) combined saccharide and polypeptide antigens are used for priming an immune response but only one is used for boosting the response.

Various timings for priming and boosting are suitable for use with the invention. In one embodiment, a priming dose is given to a child and a booster is given to a teenager (13-18 years) or young adult (19-25 years). In another embodiment, a priming dose is given to a teenager or young adult and a booster is given during pregnancy. In another embodiment, a priming dose is given to a female who intends to become pregnant and a booster is given during pregnancy.

Immunogenic pharmaceutical compositions

Polypeptide/saccharide combinations are formulated as immunogenic compositions, and more preferably as compositions suitable for use as a vaccine in humans (*e.g.* children or adults).

Vaccines of the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat disease after infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

The composition of the invention is preferably sterile.

The composition of the invention is preferably pyrogen-free.

The composition of the invention generally has a pH of between 6.0 and 7.0, more preferably to between 6.3 and 6.9 *e.g.* 6.6 \pm 0.2. The composition is preferably buffered at this pH.

Other components suitable for human administration are disclosed in reference 42.

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Preferred further adjuvants include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphosphates, orthophosphates), sulphates, *etc.* {*e.g.* see chapters 8 & 9 of ref. 43}}, or mixtures of different mineral compounds, with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption being preferred. The mineral containing compositions may also be formulated as a particle of metal salt. See ref. 44.

B. Oil-Emulsions

Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See ref. 45.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaja saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsapilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-

HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in U.S. Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO 96/33739).

5 Combinations of saponins and cholesterol can be used to form unique particles called Immunostimulating Complexs (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP 0 109 942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be
10 devoid of additional detergent. See ref. 46.

A review of the development of saponin based adjuvants can be found at ref. 47.

C. Virosomes and Virus Like Particles (VLPs)

Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or
15 formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid
20 proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Q β -phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Refs. 48, 49, 50 and 51. Virosomes are discussed further in, for example, Ref. 52

D. Bacterial or Microbial Derivatives

25 Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) *Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)*

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated
30 chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives e.g. RC-529. See Ref. 53.

(2) *Lipid A Derivatives*

35 Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in Ref. 54 and 55.

(3) *Immunostimulatory oligonucleotides*

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See ref. 56, WO 02/26757 and WO 99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides is further discussed in Refs. 57, 58, WO 98/40100, U.S. Patent No. 6,207,646, U.S. Patent No. 6,239,116, and U.S. Patent No. 6,429,199.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT. See ref. 59. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 60, 61 and WO 01/95935. Preferably, the CpG is a CpG-A ODN. Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 62, 63, 64 and WO 03/035836.

(4) *ADP-ribosylating toxins and detoxified derivatives thereof.*

Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E. coli* (i.e., *E. coli* heat labile enterotoxin "LT), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in WO 95/17211 and as parenteral adjuvants in WO 98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivatives thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in Refs. 65, 66, 67, 68, 69, 70, 71 and 72 each of which is specifically incorporated by reference herein in their entirety. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., Mol. Microbiol (1995) 15(6):1165 – 1167, specifically incorporated herein by reference in its entirety.

E. Human Immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g. interferon- γ), macrophage colony stimulating factor, and tumor necrosis factor.

F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Ref. 73) or mucoadhesives such as

cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrrolidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g., ref. 74.

G. Microparticles

5 Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150 μ m in diameter, more preferably ~200nm to ~30 μ m in diameter, and most preferably ~500nm to ~10 μ m in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a
10 negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in U.S. Patent No. 6,090,406, U.S. Patent No. 5,916,588, and EP 0 626 169.

15 I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. Ref. 75. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (Ref. 76) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol
20 (Ref. 77).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

25 PCPP formulations are described, for example, in Ref. 78 and 79.

K. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-
30 hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues, described further in Ref. 80 and 81.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified
35 above. For example, the following adjuvant compositions may be used in the invention:

- (1) a saponin and an oil-in-water emulsion (ref. 82);

(2) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) (see WO 94/00153);

(3) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) + a cholesterol;

(4) a saponin (e.g. QS21) + 3dMPL + IL-12 (optionally + a sterol) (Ref. 83);

5 combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (Ref. 84);

(5) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.

(6) RibiTM adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM); and

(7) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).

15 Aluminium salts and MF59 are preferred adjuvants for parenteral immunisation. Mutant bacterial toxins are preferred mucosal adjuvants.

The composition may include an antibiotic.

GBS polypeptide(s) and saccharide(s) in the compositions of the invention will be present in 'immunologically effective amounts' *i.e.* the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention of disease. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Typically, the compositions of the invention are prepared as injectables. Direct delivery of the compositions will generally be parenteral (*e.g.* by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue) or mucosal (*e.g.* oral or intranasal [85,86]). The compositions can also be administered into a lesion. The invention provides a syringe containing a composition of the invention.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated. The vaccines are particularly useful for vaccinating children and teenagers, and more particularly females.

As well as GBS polypeptides and saccharides, the composition of the invention may comprise further antigens. For example, the composition may comprise one or more of the following further antigens:

- antigens from *Helicobacter pylori* such as CagA [87 to 90], VacA [91, 92], NAP [93, 94, 95],
5 HopX [e.g. 96], HopY [e.g. 96] and/or urease.
- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 97 from serogroup C [see also ref. 98] or the oligosaccharides of ref. 99.
- a saccharide antigen from *Streptococcus pneumoniae* [e.g. 100, 101, 102].
- 10 – an antigen from hepatitis A virus, such as inactivated virus [e.g. 103, 104].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [e.g. 104, 105].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [e.g. refs. 106 & 107].
- 15 – a diphtheria antigen, such as a diphtheria toxoid [e.g. chapter 3 of ref. 108] e.g. the CRM₁₉₇ mutant [e.g. 109].
- a tetanus antigen, such as a tetanus toxoid [e.g. chapter 4 of ref. 128].
- a saccharide antigen from *Haemophilus influenzae* B [e.g. 98].
- an antigen from hepatitis C virus [e.g. 110].
- 20 – an antigen from *N.gonorrhoeae* [e.g. 111, 112, 113, 114].
- an antigen from *Chlamydia pneumoniae* [e.g. refs. 115 to 121].
- an antigen from *Chlamydia trachomatis* [e.g. 122].
- an antigen from *Porphyromonas gingivalis* [e.g. 123].
- polio antigen(s) [e.g. 124, 125] such as OPV or, preferably, IPV.
- 25 – rabies antigen(s) [e.g. 126] such as lyophilised inactivated virus [e.g. 127, RabAvert™].
- measles, mumps and/or rubella antigens [e.g. chapters 9, 10 & 11 of ref. 128].
- influenza antigen(s) [e.g. chapter 19 of ref. 128], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [e.g. 129].
- 30 – an antigen from *Streptococcus pyogenes* (group A streptococcus) [e.g. 3, 130, 131].
- an antigen from *Staphylococcus aureus* [e.g. 132].
- an antigen from *Bacillus anthracis* [e.g. 133, 134, 135].
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne encephalitis virus, West Nile virus.
- 35

- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- a parvovirus antigen *e.g.* from parvovirus B19.
- a prion protein (*e.g.* the CJD prion protein)
- 5 — an amyloid protein, such as a beta peptide [136]
- a cancer antigen, such as those listed in Table 1 of ref. 137 or in tables 3 & 4 of ref. 138.

The composition may comprise one or more of these further antigens.

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means [107]).

- 10 Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred. Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates are
- 15 the same as those described above for GBS saccharide conjugation, with CRM197 being preferred.

Antigens in the composition will typically be present at a concentration of at least 1µg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

- As an alternative to using protein antigens in the composition of the invention, nucleic acid
- 20 encoding the antigen may be used. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA *e.g.* in the form of a plasmid) that encodes the protein.

Methods of treating patients

- The invention provides polypeptide/saccharide combinations of the invention for use as
- 25 medicaments. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

- The invention also provides a method of raising an immune response in a patient, comprising administering to a patient a composition of the invention. The immune response is preferably protective against streptococcal disease, and may comprise a humoral immune response and/or a
- 30 cellular immune response.

The invention also provides the use of polypeptide/saccharide combination of the invention in the manufacture of a medicament for raising an immune response in an patient. The medicament is preferably an immunogenic composition (*e.g.* a vaccine). The medicament is preferably for the prevention and/or treatment of a disease caused by GBS (*e.g.* meningitis, sepsis, chorioamnionitis).

The invention also provides for a kit comprising a first component comprising the immunogenic compositions of the invention. The kit may further include a second component comprising one or more of the following: instructions, syringe or other delivery device, adjuvant, or pharmaceutically acceptable formulating solution.

5 The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated
10 immunity. The method may raise a booster response.

Process for manufacturing

The invention provides a process for preparing a composition of the invention, comprising the step of mixing (i) one or more GBS polypeptide antigens with (ii) one or more GBS saccharide antigens.

15 The process may comprise the step of covalently linking the GBS polypeptide to the GBS saccharide in order to form a conjugate.

Definitions

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

20 The term "about" in relation to a numerical value *x* means, for example, $x \pm 10\%$.

The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

MODES FOR CARRYING OUT THE INVENTION

25 GBS serotype III is grown in Todd-Hewitt broth as described in reference 36 and its capsular polysaccharide was purified. The polysaccharide is depolymerised, sized and purified as described in reference 14 to give oligosaccharide antigen. Similar procedures are used to prepare capsular polysaccharides from other GBS serotypes.

The oligosaccharide is either admixed with or covalently conjugated (directly or via a linker)
30 to purified serotype V protein. Preferably, the protein comprises a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention. All documents cited herein are incorporated by reference in their entirety.

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CLAIMS:

1. An immunogenic composition comprising a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.
2. The immunogenic composition of claim 1, wherein said GBS polypeptide antigens further comprise a GBS polypeptide or a fragment thereof of serogroup II.
3. The immunogenic composition of claim 1, wherein said GBS polypeptide antigen combination comprises GBS 80 or a fragment thereof.
4. The immunogenic composition of claim 3, wherein said GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 404, (16) GBS 80 and GBS 656, (17) GBS 80 and GBS 690, and (18) GBS 80 and GBS 691.
5. The immunogenic composition of claim 4, wherein said combination is selected from the group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147.

6. The immunogenic composition of claim 4, wherein said combination comprises GBS 80 and GBS 691.
7. The immunogenic composition of claim 1, wherein said composition comprises a combination of at least three GBS polypeptide antigens.
8. The immunogenic composition of claim 7, wherein said combination comprises GBS 80 and GBS 691.
9. The immunogenic composition of claim 7, wherein said combination comprises GBS 80.
10. The immunogenic composition of claim 1, wherein at least one GBS polypeptide antigen is covalently linked to the GBS saccharide antigen.
11. The immunogenic composition of claim 1, wherein said GBS saccharide antigen is covalently linked to a carrier protein.
12. The immunogenic composition of claim 11, wherein said carrier protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, *N. meningitidis* outer membrane protein, heat shock protein, pertusis protein, protein D from *H. influenzae*, and toxin A or B from *C. difficile*.
13. The immunogenic composition of claim 12, wherein said carrier protein is selected from the group consisting of tetanus toxoid and diphtheria toxoid.
14. The immunogenic composition of claim 13, wherein said carrier protein is a diphtheria toxoid.
15. The immunogenic composition of claim 14, wherein said diphtheria toxoid is CRM197.

16. A method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of claim 1.

17. A method for the manufacture of a medicament for raising an immune response against GBS comprising combining a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

SEQUENCE LISTING

SEQ ID NO. 1

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SEQ ID NO. 3

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SEQ ID NO. 4

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SEQ ID NO. 5

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SEQ ID NO. 6

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SEQ ID NO. 7

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SEQ ID NO. 8

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SEQ ID NO. 9

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SEQ ID NO. 10

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SEQ ID NO. 11

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SEQ ID NO. 12

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 NKPEQDGSQAPDKKPEAKPEQDGSQTPDKKKETKPEKDSGQTPGKTPQKQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT
 NRLHLLKLVMTTFFLG

SEQ ID NO. 13

ATGGGACGAGTAATGAAAAACAATAACAACATTTGAAAAATAAAAAAGTTTATGCTCTGGTTTAGCACGATCTGGAGAAGCTGCTGC
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 AAGAGGGTATTAAGTGGTTTGTGGTAGTCATCCTTTAGAATTGTTAGATGAGGATTTTTGTACATGATTAAAAATCCAGGAATA
 CCTTATAACAATCCTATGGTCAAAAAAGCATTAGAAAAACAATCCCTGTTTTGACTGAAGTGAATTAGCATACTTAGTTTCAGA
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 GAGGTTTGTAGCTGGGAATATCGGCTTTCCTGCTAGTGAAGTTGTTGAGGCTGCGAATGATAAAGATACTCTAGTTATGGAATTA
 TCAAGTTTTGAGCTAATGGGAGTTAAGGAATTTTCGTCCTCATATTGCAGTAATTACTAATTTAATGCCAACTCATTAGATTATCA
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 CAAGACAAGCAACTTTTTCTATAAAGGGGAGAATATATGTGTCAGTAGATGACATTGGTGTCAGGAAGCCATAACGTAGAGAATGC
 TCTAGCAACTATTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAACTTTAAGCAATTTTGGAGGTGTTAAAC
 ACCGCTTGCAATCACTCGGTAAAGGTTTCATGGTATTAGTTTCTATAACGACAGCAAGTCACTAATATATTGGCAACTCAAAAAGCA
 TTATCTGGCTTTTGATAATACTAAAGTTATCCTAATTGTCAGGAGGCTTTGATCGCGGTAATGAGTTTGATGAATTGATACCAGATAT
 CACTGGACTTAAACATATGGTTGTTTTAGGGGAATCGGCATCTCGAGTAAACGTCGTCACAAAAAGCAGGAGTAACCTTATAGCG
 ATGCTTTAGATGTTAGAGATGCGGTACATAAAGCTTATGAGGTGGCACAAACAGGGCGATGTTATCTTGCTAAGTCTGCAAAATGCA
 TCAATGGGACATGTATAAGAATTTGCAAGTCCGTGGTGATGAATTCATTGATACTTTTCAAGTCTTAGAGGAGAG

SEQ ID NO. 14

MGRVMKTIITTFENKKVLVLGLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCGSHPLELLEDFFCYMIKNPGI
 PYNPNMVKKALEKQIPVLTEVELAYLVSESQILIGITGSNGKTTTTMTIAEVLNAGGQRLLAGNIGFPASEVQQAANDKDLVMEI
 SSFQLMGVKEFRPHIAVITNLMPTHLDYHGSFEDVAAKWNINQNMSSSDFLVLFNFGISKEIAGTTKATIVPFTSEKVDGAYV
 QDKQLFYKGENIMSVDDIGVPGSHNVENALATIYAVAKLAGISNQVIRETLNFGVGVKHLQSLGKVHGISFYNDKSTNILATQKA
 LSGFDNTKVLIIAGGLDRGNEFDELIPDITGLKHMVVLGESASRVKRAAQKAGVTYS DALDVRDAVHKAYEVAQQGDVILLSPAN
 A SWDMYKNFEVRGDEFIDTFESLRGE

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTTAACTAGTGGTGGTGACGCCCCCTGGTATGAACGCTGCTATCCGTGCAGTTGTTGCTAAAGCAATTTCTGAAGGTATG
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 GGAACGTTTTTACGTTTCAGCACGTTATCCTGAATTTGCTGAACCTGAAGGTGAGCTTAAAGGGATTGAACAGCTTAAAAACACGGTATTGAAGGT
 GTAGTAGTTATCGGTGGTGATGGTTCTTATCATGGTGCTATGCGTCTAACTGAGCACGGTTTCCAGCTGTTGGTTTGGCGGGTACAATTGATAAC
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 AACGAAGAAATGGTTGAAAGTCCAATTTAGGTTTAGCAGAGAAGGTCCTTTGTTGAGCTTGATGATGAAGGAAAAATCGTTGTTAATAATCCG
 CATAAAGCGGACCTTCGCTTGGCAGCACTTAATCGTGACCTTGCCAACCAAGTAGTAAA

SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYGMVTDIFPLDANSVGDITINRGGTFILRSARYPEFALEGQLKGIEQLKKHIGIEG
 VVVIGGDSYHGAMRLTEHGFPAVGLPGTIDNDIVGTDYITIGFDTAVATAVENLDRLDTSASHNRTFVVEVMGRNAGDIALWSGIAAGADQIIIVP
 EEEFNIDEVVSNNVRAGYAAKGHHQIIVLAEGVMSGDEFAKTMKAAGDBDLRVNGLHLRGGSPARTDRVLASRMGAYAVQLLKEGRGGLAVGVH
 NEEMVESPIGLAEBEGALFSLTDEGKIVVNNPHKADRLRLAALNRDLANQSSK

SEQ ID NO. 17

ATGAATAAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTTCAAGCACAAGAAACAGATACGACGTTGGACAGCA
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 GCAATGTCAATTGATATGAATGTCTTAGCAAAAATAAATAACATTGCAGATATCAATCTTATTTATCCTGAGACAACACTGACAGTAACCTTACGAT
 CAGAAGAGCTCATCTGCCACTTCAATGAAAAATAGAAACACCAGCAACAAATGCTGCTGGTCAAACAACAGCTACTGTGGATTGAAAACCAATCAA
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 AACATTTTATATGTTTATCTGGCAACAAAAGTTTACTCAAAATCAAAACAGTATTATTGGACCTGCTAATACTTGGAAATGCAATGCCAGATCGTGGT
 .GGCGTTACTGCCAACCACATATGACCAGTTTACGTATCATTAAACAAATAATATAAAAAAGGAAGCTATTTGGCTCTTTTTTATATATGCTTGAAT
 AGACTTTCAAGGTTCTTATATAATTTTATTA

SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETD TTWTARTVSEVKADLVKQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIY PETTLTVTYD
 QKSHTATSMKIEPATNAAGQT TATVDLKTNQVSVADQKVS LNTI SEGMTPEAATTIVSPMKTYSSAPALKSKEVLAQEQAVSQAAANEQVSPAPV
 KSITSEVPAAKEEVKPTQTSVSQSTTVSPASVAAETPAPVAKVAPVRTVAAPRVASVKVVT PKVETGASPEHVSAPAVPVTTTSPATDSKLQATEV
 KSVPVQAQKAPTATPVAQPASTTNAVAHPENAGLQPHVAAYKEKVASTYGVNEFSTYRAGDPGDHKGGLAVDFIVGTNQALGNKVAQYSTQNMAAN
 NISYVIWQQKFYSNTNSIYG PANTWNAMPDRGGVTANHYDHVHVSFNK

SEQ ID NO. 19

ATGAAAAAGAAAATTATTTTGAAGTAGTGTCTTGGTTTÀGTCGCTGGGACTTCTATTATGTTCTCAAGCGTGTTCGCGGACCAAGTCGGTGTCT
 CAAGTTATAGGCGTCAATGACTTTCATGGTGCACTTGACAATACTGGAACAGCAAATATGCCTGATGGAAAAGTTGCTAATGCTGGTACTGCTGCT
 CAATTAGATGCTTATATGGATGACGCTCAAAAAGATTTCAAACAACTAACCCCTAATGGTGAAAGCATTAGGGTTCAAGCAGGCGATATGGTTGGA
 GCAAGTCCAGCCAACCTCTGGGCTTCTTCAAGATGAACCACTGTCAAAAATTTTAAATGCAATGAATGTTGAGTATGGCAGATTGGGTAACCATGAA
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SEQ ID NO. 20

MKKKIILKSSVLGLVAGTSIMFSSVFADQVGVQVIGVNDPHGALDNTGTANMPDGKVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
 ASPANSGLLQDEPTVKNFNAMNVEYGT LGNHEFDEGLAENRIIVTGKAPADPSNINNITKSY PHEAAKQEIIVANVIDKVNKQI PYNWKPIAIKNI
 PVNNKSVNVGFIGIVTKDIPNLVLRKNYEQYEFLEAETIVKYAKELQAKNVKAIIVLHVLPATSKNDIAEGEAAEMMKVNQLFPENSVDIVFAG
 HHNQYTNGLVGKTRIVQALSQKAYADVRGVLDTDTQDFIETPSAKVIAVAPGKKTGSADIQAIVDQANTIVKQVTEAKIGTAEVSVMITRSVDQD
 NVSPVSGSLITEAQLAIARKSWPDIDFAMTNNGGIRADLLIKPDGTTIWGAQAQVQPFNGNILQVVEITGRDLYKALNEQYDQKQNFLLQIAGLRYTY
 TDNKEGGEETPFKVVKAYKSNGEENPD AKYKLVINDFLFGGGDGFASFNRNAKLVAINPDTEVFMAYITDLEKAGKKVSPNNKPKIYVTMKNV
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 FGVGLIGIALNTKKHKMK

SEQ ID NO. 21

ATGAATAAACGCGTAAAAATCGTTGCAACACTTGGTCTCGCGTTGAATTCGGTGGTGGTAAGAAGTTGGTGAGTCTGGATACCTGGGGTGAAAGC
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 CAAGGAGCTCTGATGGCTACTGTTTCGTAAGCAGAAAGAGATTGCAGGACAAAAAGTTGGCTTCTCCTTGATATAAGGACCTGAAAATTCGTACA
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SEQ ID NO. 22

MNKRKIVATLGPVAFVFRGGKKFGESGYWGESLDVEASAEKIAQLIKEGANVFRFNFSHGDAEQGARMATVRKAEIAGQKVGFLLDTKGPEIRT
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IPFPALAEARNADIRFLEQLNFIAISFVRTAKDVNEVRAICEETGXGHVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVPPFEMVVPVYQ
 KMIITKVNAGKAVITATNMLETMDKPRATRSEVSDVFNVAIDGTDATMLSGESANGKYPVESVRTMATIDKNAQTLLENEYGRLDSSAFPRNNKT
 DVIASAVKDATHSMDIKLVVITITETGNTARAI SKFRPDADILAVTFDEKVQRSLMINWGVIPVLADKPASTDMMFEVAERVALEAGFVESGDNIVI
 VAGVPVGTGGTNTMRVRTVK

SEQ ID NO. 23

TTGCTCGCTATAATAGACAAAAAGGTGGTGATATTTATGTATTTAGCATTAATCGGTGATATCATTAATTCAAACAGATACTTGA
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SEQ ID NO. 24

MSAIDKKVVFIMYLALIGDI INSKQILERETFQOSFQQLMTELSDVYGEELISPFITITAGDEFQALLKPSKVFQIIDHILQLALKPVNVRFGLGTG
 NIITSINSNESIGADGPAYWHARSAINHIHDKNDYGTVQVAICLDDQNLLETLNLSISAGDFIKSKWTTNHFQMLEHLILQDNYQEQQHQKLAQ
 LENIEPSALT KRLKASGLKIYLRTRTQAADLLVKSCTQTQKGSYDF

SEQ ID NO. 25

ATGTTTTATACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGGTAACATAGCAGAGCTCATGATCCAAACGGAAATTGAAATGACT
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 GGGGAA

SEQ ID NO. 26

MFYTIEELVEQANSQHKGNIAELMIQTIEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGGDAVKMDQYLQSGKTI SDTTILAAVRN
 AMAVNELNNAKMLVCAPTAGSAGCLPAVISTATEKLNLTBEEQLDFLFTAGAFGLVIGNNASISGABGGCQAEVGSASAMAAAALVMAAGGTPFQ
 ASQAIAFVIKNMLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSSLPATFRETAEGGLAATPTGRRYSKEIF
 GE

SEQ ID NO. 27

ATGAGCGTATATGTTAGTGGAATAGGAATTATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTCGACTTAAAGAAGGAATTT
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SEQ ID NO. 28

MSVYVSGIGIISLKGNYSEHKQHLFDLKEGISKHLYKNHDSILESYSITSDPEVPEQYKDETRNFKFAFTAFEEALASSGVNLKAYHNIACVLG
 TSLGGKSAGQNALYQFEEGERQVDASLLEKASVYHIADELMAYHDIVGASYVISTACSAASNNAVILGTQLLDGDCDLAICGGCDELSDISLAGFTS
 LGAINTEMACQPYSSGKGINLGEAGFVVLVKDQSLAKYKGIIGGLITSDGYHITAPKPTGEGAAQIAKQLVTQAGIDYSEIDYINGHGTGTQANDK
 MEKNMYGKFPTTTLLSSTKGQTHLGAAGIIELINCLAAIEEQVTPATKNEIGIEGFPENFVYHQKREYPIRNALNFSFAGGNNNSGVLLSSLD
 PLETLPARENLKMALSSVASISKNESLSITYEKVASNFNDFEALRFKGARPPKTVNPAQFRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGIV
 FTTLSGPVEVVEGIEKQITTEGYAHVSASRFPFTVMNAAAGMLSIIFKITGPLSVISTNSGALDGIQYAKEMMRNDNLDYVILVSNQWTDMSFMWW
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 MPNLASGQFGFSSNGAGEELDYTVNESIEKGYLLVLSYSIFGGISFAIEKR

SEQ ID NO. 29

ATGAAATAGATGACCTAAGAAAAAGCGACAATGTTGAAGATCGTCGCTCCAGTAGCGGAGGTTTCATCTCTAGCGGAGGAAGTGGATTACCGATT
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 AAAGAAACCTACGGAATTTAGTGCTGATAGCTTTACCCATGGAACAGCTGAACAACGCCAACGTTGGTTTAAACAAGGCTTTCAATATGGTGAC
 ATCCAACACGGTGATACTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKSNDVEDRRSSSGSSGSLPILQLLLLRGSKTKLVLLIILLGGGLTSIFNDSSSPSSYQSQNVRSRVDNSATREQIDFVNK
 VLGGTEDFWSQEFQYQGFNGYKEPKLVLYTNSIQTGCGIGESAGSFPYCSADKKIYLDISFYNELSHKYGATGDFAMAYVIAHEVGHIIQTELIM
 DKYNMRHGLTKKEANLNVRLQLADYYAGVWAHYIRGNLLEQGDFFBAMNAHAVGDDTLQKETYGKLVPSDFTHGTAEQRQRWFNKGFGQYGD
 IQHGDFTFSVEHL

SEQ ID NO. 31

ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAACGTA
 ACGCCGATAGTACATGCTGATGTCAATTCTGTTGATACGAGCCAGGAATTTCAAATAATTTAAAAATGCTATTGGTAACCTACCATTTCAA
 TATGTTAATGGTATTTATGAATTAATAATAATCAGACAAATTTAAATGCTGATGTCAATGTTAAAGCGTATGTTCAAATACAAATGACAATCAA
 CAAAGACTATCAACTGCTAATGCAATGCTTGATAGAACCATTCGTCATATCAAATCGCAGAGATACCACTCTTCCCGATGCAAATGGAAACCA
 TTAGGTTGGCATCAAGTACTAATGACCATTTATGGACATGCAAGTTCGACAAAGGGGCAATTAATGGCTATGCTTTAGCTGGAAATTTCAAAGGT
 TGGGATGCTTCCGTGTCAAATCCTCAAATGTTGTACACAAACAGCTCATTCCAACCAATCAAATCAAAAAATCAATCGTGGCAAAATATTATTAT
 GAAAGCTTAGTTTCTGAAGCGGTTGACCAAAACAAACGTTGCTTACCGTGTAATCCATTGTACCGTAATGATAGTATTAGTTCCATTGCA
 ATGCACCTAGAAGCTAAATCAAGAATGGCACATTAGAATTTAATGTTGCTATTCCAAACACACAAGCATCATACACTATGGATTATGCAACAGGA
 GAAATAACACTAAAT

SEQ ID NO. 32

MKRLHLKFTITVIATLGLMGLVMTFGLPTQPNVTPIVHADVNSSVDTSQEFQNNLKNIAIGNLPFYVYVNGIYELNNQTNLNADVNKAYVQNTIDNQ
 QRLSTANAMLDRTIRYQNRDITLDPANWKPLGWHQVATNDHYGHAVDKGHLIAYALAGNFKGWDASVSNPQNVVTQTASHNSQNKINRGQNY
 ESLVRKAVDQNKVRVRYVTPLYRNDITLVPFAMHLEAKSQDGTLEFNVAIPNTQASYTMDYATGEITLN

SEQ ID NO. 33

ATGAGTAAACGACAAAATTTAGGAATTAGTAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATTGTAGTAATAGGTGGCTTTTATGG
 GTACAATCTCAACCTAATAAGAGTGCGAGTAAAACTAACTACAAAGTTTAAATGTTAGAGAAGGAAGTGTTCGTCCTCAACTCTTTTGACAGGA
 AAAGCTAAGGCTAATCAAGAACGATATGTGATTTTGTGCTAATAAAGGTAATCGAGCAACTGTACAGTTAAAGTGGGTGATAAATCACAGCT
 GGTGAGCAGTTAGTTCAATATGATACAACTGCACAGCAGCCTACGACACTGCTAATCGTCAATTAATAAAGTAGCGCGTCAGATTAAATAAT
 CTAAGACCAACAGGAAGTCTTCCAGCTATGGAATCAAGTGATCAATCTTCTCATCATCACAGGACAAGGGACTCAATCGACTAGTGGTGCGACG
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 CAGGCTGTTAAAAATAAAATCTAAGGCTATCCTGACAGGAATGGGAAGGTAAATTTCAATATATCTCAAATTTATCCAGAAGCAGAAGCAAAACAA
 AATGACTCTAATAACGGCTCTAGTGCTGTAAATATAAATAAAGTAGATATTACTAGCCCTCTCGATGCATTAAACAAGGTTTACCGTATCA
 GTTGAAGTAGTTAATGGAGATAGCACCTTATTGTCCCTACAAGTTCTGTGATAAACAAGATAATAAACACTTTGTTTGGGTATACAAATGATTCT
 AATCGTAAAAATTTCAAAGTTGAAGTCAAATTTGGTAAAGCTGATGCTAAGACACAAGAAATTTTATCAGGTTTGAAGCAGGACAAATCGTGGT
 ACTAATCCAAGTAAACCTTCAAGGATGGGCAAAAAATTGATAATATTGAATCAATCGATCTTAACCTAATAAGAAATCAGAGGTGAAA

SEQ ID NO. 34

MSKRQNLGISKKGAIISGLSVALIVVIGGFLWVQSQPNKSAVKNTYKVFNVREGSVSSSTLLTGKAKANQEYVYFDANKGNRATVTVKVGDKITAG
 QQLVQYD'TTAAQAYDTANRQLNKVARQINNLLKTTGSLPAMESSDQSSSSSQGGQTQSTSGATNRLQQNYQSQANASYNQQLQDLNDAYADAQAEVN
 KAQKALNDT'VITSDVSGTVVEVNSDIDPASKTSQVLVHVATEGKLQVQGTMSYDLANVKKDQAVKIKSKVYDPKEWEGKISYISNYPEABANNND
 NNGSSAVNYKYKVDIT'SPLDALKQGF'TVSVVEVNGDKHLIVPTSSVINKDNKHFVWVYNDNSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTNPS
 KTFKDGQKIDNIESIDLNSNKKSEVK

SEQ ID NO. 35

ATGAAAAAATTGGAATTAT'TGTCCTCACACTACTGACCTTCTTTTGGTATCTTTCGGGACAACTAAACAAGAAAGCACTAAAACAACTATT
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 CCAACTTTAGTTATTAATATGGTGCACAAATATT'TAGATATGATGCCAGCCTTGGGGAAAGTATTCGGTAAAGAAAAAGAGCTAATCAGTGG
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 TCTGACCCCTCTATCTTTAGAAGCTCAATTAATAATCATTTACAAGGCTATCAAGAAAAATACAAAT

SEQ ID NO. 36

MKKIGIIVLTLTFFLVSCGQQTQESTKTTISKMPKIEGFTYYGKIPENPKVINFTYSYTGYYLLKLGVNVSSYSLDLEKDSVPF
 GKQLKEAKKL'TADDTEAIAAQKPDLMVFDQDPNINTLKKIAPT'LVIKYGAQNYLDMMPALGKVFGEKEANQWVSQWKTKTLAVK
 KDLHHILKPN'TFTIMDFYDKNI'LYLGNFNGRGGELIYDSLGYAAPEKVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKT'TKKA
 SSLKESDVWKNLPAVKKGHIIESNYDVFYFSDPLSLEAQLKSFTKAIKENTN

SEQ ID NO. 37

ATGAAAGTGAAAAATAAGATT'TAACGATGGTAGCACTTACTGTCTTAACATGTGCTACTTATTCATCAATCGGTATGCTGATACAAGTGATAAGA
 ATACTGACACGAGTGTCTGACTACGACCTTATCTGAGGAGAAAAAGATCAGATGAAGTAGACCACTAGTACTGGTTCTTCTCTGAAATGAATC
 GAGTTCATCAAGTGAACCGAGAAACAAATCCGTCAACTAATCCACTACACAGAACCATCGCAACCTCACCTAGTGAAGAGAACAGCCTGATGGT
 AGAACGAAGACAGAAATTGGCAATAATAAGGATATTTCTAGTGAACAAAAGTATTAATTCAGAAAGATAGTATTAAGAAATTTAGTAAAGCAAGTA
 GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAAGCAAAATGATGGGAAAAAGGCCACAGTAAGCCTAAAAAGGAATTCCTAAAC
 AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGGATTATCTGTTATCATTAAGTTTTTACAATAAGAAATGAAGCTTTAT

SEQ ID NO. 38

MKVKNKILTMVALT'VLTCATYSSIGYADTSDKNTDTSVTTTTLSEEKRSDELQSSSTGSSSENESSSSSEPETNPSTNPPTTESQPSPPSEENKPD
 RTKTEIGNNKDISSGTVLISEDSEIKNFSKASSDQEEVDRDESSSSKANDGKKGHSKPKKELPKTGDSHSDTVIASTGGIILLSLSFYNKKMKLY

SEQ ID NO. 39

ATGAAAAGGATACGGAAAAGCCTTATTTTGTCTCGGAGTAGTTACCTTAATTTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAATGGCT
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 ACCTAAATTAGCTCAAGCAGTAGCTTACGCTACTCGAGTTAAATTTGCAAGTTTAAAGTCC'TTARAAGCAGTTCCCAAAAAACAATAAGATTACTTA
 GAAAATTTGAAACTAATCTTAAGGTACTTGTCAAATCGTTAAATCAATAG

SEQ ID NO. 40

MKRIRKSLIFVLGVVTLICLCACTKQSQKNGLSVVTSFYVPVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAAIYDADFLYHSHTLEAWARR
 LEPSLHHSKVS'VIEASKGMTLDKVHGLEDVAEKGVDESTLYDPHTWNDPVKVSEEAQLIATQLAKKDPKNKVVYQKNADQFSDKAMAIIEKYKPKF
 KAAKSKYFVTSHTAFSYLAKRYGLTQLGIAGVSTEQEPSAKKLAEIQEFVKTYKVKTI'FVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL
 ENLETNLKVLVKSINQ

SEQ ID NO. 41

ATGCCTAAGAAGAAATCAGATACCCAGAAAAAGAAAGTTGTCTTAACGGAATGGCAAAAGCGTAACCTTGAATTTTAAAAAACGCAAGAAG
 ATGAAGAAGAACAAAAACGTATTAACGAAAAATACGCTTAGATAAAAGAAAGTAAATTAATATTTCTCTCTCTGAAGAACCTCAAATACTACTAA
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 GTGGAAATCAGCATACCTGATGATATTTGATAGAGAAACGAATATTCAAAAAACGATTATTTCTTTTCTTTAATTTTAAACATAAGCTAT
 TGAACAACGTTTAGCTGCAGAAGATGTATGGGTAAAAACAGCTCAGATGACTTATCAATTTCCCAATAAGTTTCATATCAAGTTCAAGAAAAATAG

ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGGAAGCTGGAAAAAGGCTGATCCTGTAAATAGTTCAGAGCTACCAAAGCACT
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AAGTTTAGCTGATTCTAAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGGAATAGTATTAGAATACCATTATCTAAATTTAAAGAAAGA
CTTCCTTTTTACAAACAAATTAAGAAGAACCTTAAGGAACCTTCTATTGTTGATATGGAAGTGGGAGTTTACACAACAACAAATACCATTGAATCAA
CCCCGTGTTAAAGCAGAAGATACAAAAATAAATCAACTGATAAAACACAAACACAAATGGTCAGGTTGCGGAAAATAGTCAAGGACAAACAAATAA
CTCAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCTCAAATGTTAAT

SEQ ID NO. 42

MPKKKSDTPEKEEVVLTEWQKRNLEFLKKRKEDEEEQKRINEKLRLDKRSKLNISPEEPQNTTKIKKLHFPKISRPKIEKKQKKKEKIVNSLAKTNR
IRTAPIFVVAFLVLVSVFLLTPFSKQKTIITVSGNQHTPDILIEKTNIQNDYFFSLIFKHKAIEQRLAEDVWVKTAQMTYQFPNKFHIQVQENK
IIAYAHTKQGYQPVLETGKKADPVNNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVITSLADSKTTPDLLLLDMHDGNSIRIPLSKFKER
LPFYKQIKKNLKEPSIVDMEVGVTNTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGGTNNNSNTNQGGQIATEQAPNPQNVN